SEPTEMBER 1992 VOL 68 No 3

BRITISH HEART JOURNAL

In association with the British Cardiac Society

Editorials

253 Graft vascular disease in heart transplant patients *J Mann*
255 Coronary artery disease after heart transplantation: clinical aspects *C D Scott, J H Dark*
257 Ventricular remodelling after myocardial infarction *M A Vannan, D J E Taylor*

Original articles

260 Coronary occlusive disease and late graft failure after cardiac transplantation *P A Mullins, N R Cary, L Sharples, J Scott, D Aravot, S R Large, J Wallwork, P M Schofield*
266 Impairment of coronary flow reserve in orthotopic cardiac transplant recipients with minor coronary occlusive disease *P A Mullins, A Chauhan, L Sharples, N R Cary, S R Large, J Wallwork, P M Schofield*
272 Nuclear magnetic resonance spectroscopy of excised human hearts *F Brunotte, B Peiffert, J M Escanye, G Pinelli, J Zamorano, P M Walker, J Robert, J P Villemot*
276 Intravascular ultrasound imaging of the coronary arteries: an in vitro evaluation of measurement of area of the lumen and atheroma characterisation *M H Anderson, I A Simpson, D Katritsis, M J Davies, D E Ward*
282 Lower threshold for adenosine-induced chest pain in patients with angina and normal coronary angiograms *B Lagerqvist, C Sylvén, A Waldenstrom*
286 Detection of myocardial ischaemia by transthoracic leads in ambulatory electrocardiographic monitoring *C M Jespersen, V Rasmussen*
291 Optimal control of myocardial ischaemia: the benefit of a fixed combination of atenolol and nifedipine in patients with chronic stable angina *H El-Tamimi, G J Davies*
296 Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing "athlete's heart" from hypertrophic cardiomyopathy *J F Lewis, P Spirito, A Pelliccia, B J Maron*
301 Protrusion of the device: a complication of catheter closure of patent ductus arteriosus *J Ottenkamp, J Hess, M D Talsma, T N Buis-Liem*
304 Subclinical cardiomyopathy in Becker muscular dystrophy *S E Steare, V Dubowitz, A Benatar*
309 Influence of cardiopulmonary bypass on water balance hormones in children *M Burch, L Lum, M Elliott, N Carter, D Slater, A Smith, A Ationu*
313 Magnetic resonance imaging of hearts with atrioventricular valve atresia or double inlet ventricle *I C Huggon, E J Baker, M N Maisey, A P Kakadekar, P Graves, S A Qureshi, M Tynan*
320 Successful repair of pulmonary atresia with ventricular septal defect without the use of a conduit: a new surgical option: Report of two cases *Z Al-Halees, O Galal, N Wilson*

Case reports

323 Fabry's disease with complete atrioventricular block: histological evidence of involvement of the conduction system *Y Ikari, K Kuwako, T Yamaguchi*
326 Right-sided endomyocardial fibrosis with recurrent pulmonary emboli leading to irreversible pulmonary hypertension *P A Ribeiro, R Muthusamy, C M G Duran*
330 Anomalous origin of the right coronary artery from the pulmonary artery in association with congenital aneurysm of the sinus of Valsalva: angiographic diagnosis of a rare association *A S Sundar, K A A Fox*

Technology

333 Cardiac assistance from skeletal muscle: a critical appraisal of the various approaches *S Salmons, J C Jarvis*

British Cardiac Society

339 Surgical cover for percutaneous transluminal coronary angioplasty *The Council of the British Cardiovascular Intervention Society*
342 **Letters to the editor**
343 **British Cardiac Society newsletter**
344 **Notice**

BMJ PUBLISHING GROUP

CUR-H05926-4-P25748

P, 25,748

BRITISH HEART JOURNAL

In association with the British Cardiac Society
A Registered Charity

Editor: M J Davies
Associate Editors: Kim Fox, Peter Mills
Assistant Editors: Barry R Keeton (paediatric cardiology), Edward Rowland (electrophysiology)
Technical Editor: Jane Dawson
Editorial Assistant: Pam Kendall

EDITORIAL COMMITTEE

Roger M Boyle
Stuart M Cobbe
Keith Dawkins
John L Gibbs
Roger Hall
Alan B Houston
Stewart Hunter
Michael Marmot
R Gordon Murray
John Sanderson
Tom Treasure
David E Ward
Peter Wilde
Editor: *BMJ*
Editor: *Cardiovascular Research*

NOTICE TO CONTRIBUTORS

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, 9 Fitzroy Square, London W1P 5AH, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;296:401–5). **Authors are asked to complete a copy of the checklist provided (1992;67:118–9 (January issue)) when submitting their manuscripts for publication.** The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with wide margins.)

ETHICAL STANDARDS

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

REFERENCES must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

UNITS OF MEASUREMENT

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

TABLES must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

ILLUSTRATIONS (for general requirements, please refer to *Br Heart J* 1984;51:1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible

Echocardiograms: All unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

COPYRIGHT PERMISSION to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

PROOFS of articles accepted for publication will be sent for the author's approval Proof corrections should be kept to a minimum.

NOTICE TO SUBSCRIBERS

British Heart Journal is published monthly. The annual subscription rates are £156.00 (USA $255·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £293.00 (USA $521·00). Orders should be sent to the Subscription Manager, *British Heart Journal*, BMJ Publishing Group, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($230 00) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1992 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

ISSN 0007–0769

Published by the
BMJ Publishing Group and
printed in England by
Eyre & Spottiswoode Ltd,
London and Margate

Second class postage paid, Rahway NJ Postmaster. send address changes to. British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA

British Hea Journal.

ISTIN is a once daily calcium antagonist that controls blood pressure for a full 24 hours.[1]

Additionally, ISTIN provides full 24 hour cover for your angina patients.[2]

With a smooth plasma profile over 24 hours ISTIN avoids rapidly changing plasma levels[3] resulting in a low level of early vasodilator side-effects.[4]

Istin*

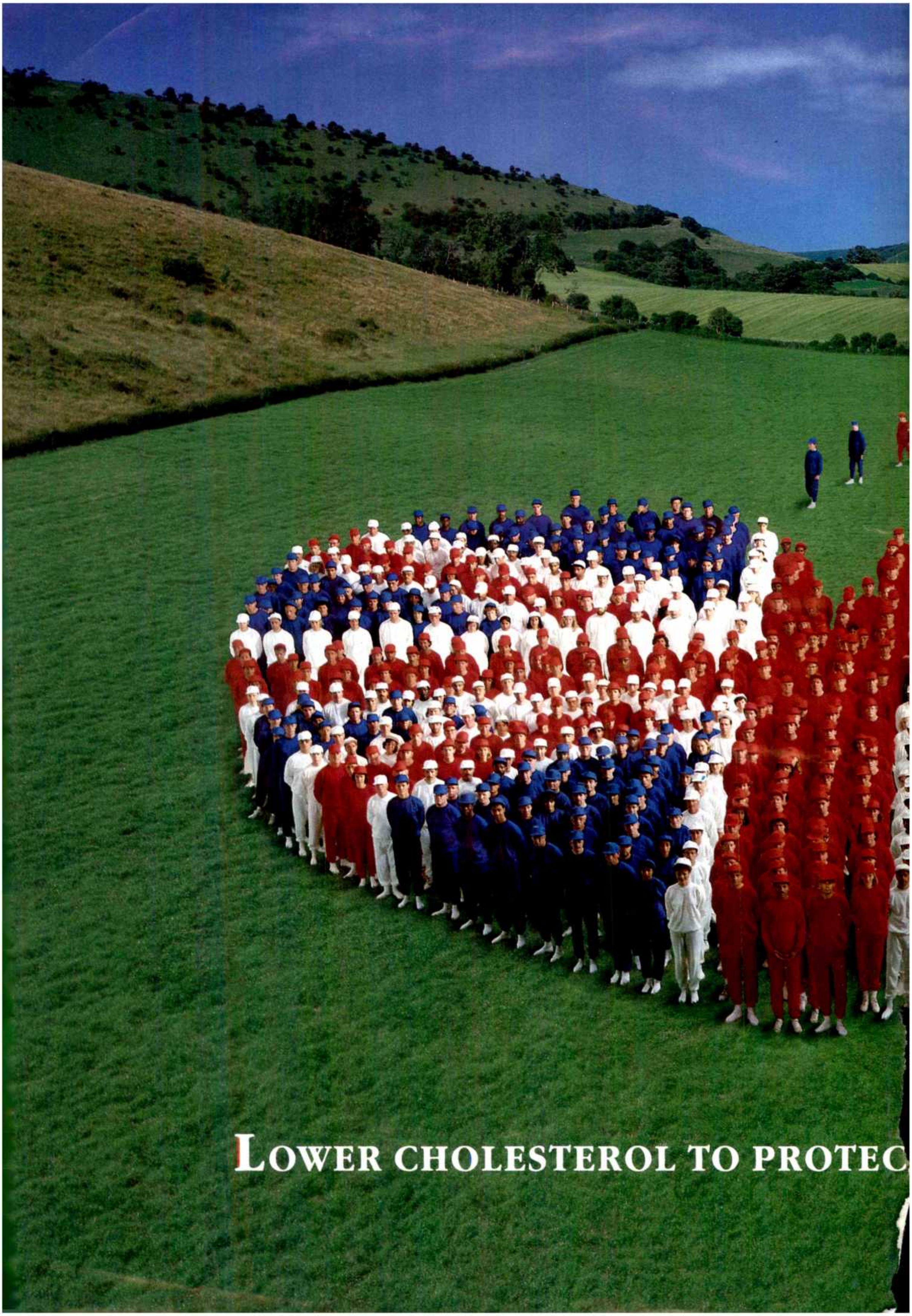
AMLODIPINE

A USER FRIENDLY CALCIUM ANTAGONIST

REVIATED PRESCRIBING INFORMATION FOR ISTIN*. INDICATIONS: FIRST-LINE TREATMENT HYPERTENSION AND MYOCARDIAL ISCHAEMIA ASSOCIATED WITH STABLE ANGINA PECTORIS OR VASOSPASTIC (PRINZMETAL'S OR VARIANT) ANGINA. **DOSAGE:** FOR HYPERTENSION AND ANGINA, AL DOSAGE 5MG ORALLY ONCE DAILY WHICH MAY BE INCREASED TO A MAXIMUM DAILY GE OF 10MG. **USE IN CHILDREN:** NOT RECOMMENDED. **USE IN THE ELDERLY:** NORMAL GE. **USE IN RENAL IMPAIRMENT:** NORMAL DOSAGE. **USE IN HEPATIC IMPAIRMENT:** GE RECOMMENDATIONS HAVE NOT BEEN ESTABLISHED; USE WITH CAUTION. **CONTRA-ATIONS:** KNOWN SENSITIVITY TO DIHYDROPYRIDINES. **WARNINGS AND PRECAUTIONS:** NANCY AND LACTATION: ISTIN SHOULD NOT BE ADMINISTERED DURING PREGNANCY OR LACTATION, OR TO WOMEN OF CHILD-BEARING POTENTIAL UNLESS EFFECTIVE CONTRACEPTION IS USED. **SIDE-EFFECTS:** HEADACHE, OEDEMA, FATIGUE, NAUSEA, FLUSHING, AND DIZZINESS. **PACKAGE QUANTITIES AND BASIC NHS COST:** 5MG TABLETS CALENDAR PACK OF 28 £11.85 (PL 0057/0297); 10MG TABLETS CALENDAR PACK OF 28 £17.70 (PL 0057/0298). FURTHER INFORMATION ON REQUEST. **PFIZER LIMITED**, SANDWICH, KENT. **REFERENCES:** **1.** MROCZEK WJ, BURRIS JF AND ALLENBY KS, J CARDIOVASC PHARMACOL, 1988, **12** (SUPPL 7): S79-S84. **2.** TAYLOR CR ET AL, PRESENTED AT A SYMPOSIUM ON CIRCADIAN VARIATION IN CARDIOVASCULAR DISEASE: THE NEED FOR COMPLIANCE, SEPTEMBER 1990. **3.** DATA ON FILE: PFIZER PROTOCOL 368. **4.** OSTERLOH I, AM HEART J, 1989, **118**: 1114-1120.

e Mark

60580


LOWER CHOLESTEROL TO PROTEC

HE HEART OF THE NATION

- In 1989, coronary heart disease caused 26% of all deaths in England, Wales, and Scotland.[1]
- 1% reduction in cholesterol reduces coronary heart disease by 2%.[2]
- The EAS/BHA goal of treatment: <5.2 mmol/l.
- 'Zocor' is indicated in patients with primary hypercholesterolaemia with a cholesterol level of 6.5 mmol/l or greater and resistant to dietary control.

THE 1991
UK PRIX GALIEN
SPECIAL COMMENDATION

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

INDICATIONS Primary hypercholesterolaemia unresponsive to diet with a cholesterol level of 6.5 mmol/litre or greater.

DOSAGE AND ADMINISTRATION Initially 10 mg *nocte*; dose range 10-40 mg once daily *nocte*. Maximum therapeutic response occurs within four to six weeks. Consider dose reduction if total serum cholesterol level falls below 3.6 mmol/l or if LDL cholesterol falls below 1.94 mmol/l. (See Data Sheet for full dosage instructions.) A standard cholesterol-lowering diet should be continued. *Concomitant therapy:* 'Zocor' is effective alone or in combination with bile-acid sequestrants. Lowest recommended dose should be used with immunosuppressants. *Impaired renal function and elderly patients:* Modification of dose should not be necessary. *Children:* Studies to show safety and efficacy have not been done.

CONTRA-INDICATIONS Hypersensitivity to this product; active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and breast-feeding; women of child-bearing potential unless adequately protected by non-hormonal methods.

PRECAUTIONS *Homozygous familial hypercholesterolaemia:* 'Zocor' is unlikely to be effective. *Hypertriglyceridaemia:* 'Zocor' is not indicated where hypertriglyceridaemia is the abnormality of most concern. *Hepatic effects:* Initial and periodic liver function monitoring recommended. Discontinue if persistent enzyme elevations occur, particularly if they rise to three times the upper limit of normal. Caution in patients with a history of liver disease and/or alcoholism. *Muscle effects:* Clinically insignificant transient mild elevations of creatine phosphokinase have been seen. Therapy with 'Zocor' should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected. *Pregnancy:* Contra-indicated. One month should elapse between ending therapy with 'Zocor' and planned conception. *Drug interactions:* Care should be taken in patients on concomitant lipid-lowering therapy, particularly fibrates or nicotinic acid derivatives or immunosuppressive therapies.

SIDE EFFECTS Side effects reported in controlled clinical trials: abdominal pain, constipation, flatulence, asthenia, and headache. Rarely, myopathy. Side effects reported either in long-term extension studies or in marketed use: nausea, diarrhoea, rash, dyspepsia; and rarely, rhabdomyolysis and hepatitis. Isolated cases of angioneurotic oedema also have been reported.

BASIC NHS COST 10mg tablets, £18.29 for 28-tablet calendar pack. 20mg tablets, £31.09 for 28-tablet calendar pack.

Product licence numbers: 10mg tablets, 0025/0241.
20mg tablets, 0025/0242. Issued December 1991.

® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA

REFERENCES
1. OPCS Monitor DH2, June 1990.
2. Lipid Research Clinics Program. *J. Amer. med. Ass.*, 1984, **251**, 351.

Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU

MSD
MERCK SHARP & DOHME

ZOCOR®

(simvastatin, MSD)

Reducing cholesterol to help prevent coronary heart disease

12-92 ZCR 91.GB 7571

In hypertension compliance can never be guaranteed because there are no painful symptoms to act as a reminder.

Consequently the simpler the dose the better the chances of compliance.[2]

A SINGLE DOSE OF ADALAT CAN NOW LAST RIGHT ROUND THE CLOCK.[1]

That's why new Adalat LA30 has been designed to be taken simply once a day.[1]

And due to its slower absorption, more gradual action, and lower peak plasma concentrations[1], it has a favourable side-effect profile.[3]

THE NEW ONCE-DAILY
Adalat® LA30
nifedipine 30mg

ABRIDGED PRESCRIBING INFORMATION (Refer to full data sheet before prescribing) **Presentation:** Pink lacquered tablets each containing 30mg or 60mg nifedipine in a controlled release formulation, one side marked Adalat 30 or Adalat 60. **Indications:** Mild to moderate hypertension. **Dosage and Administration:** Adalat LA tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up. One 30mg tablet once daily swallowed whole with a glass of fluid to be taken at approximately 24 hour intervals, preferably during the morning. Dosage can be increased according to individual requirements up to a maximum of 90mg once daily. Patients controlled on Adalat capsules or Adalat Retard may be safely switched to Adalat LA at the recommended initial dose of 30mg once daily, with subsequent titration to a higher dose as clinically warranted. *Renal impairment* Dosage adjustment should not be necessary. *Elderly* Dosage adjustment not usually necessary. *Children* No recommendations for use. **Contra-indications, warnings etc. Contra-indications:** Known hypersensitivity to nifedipine; women of child-bearing potential and nursing mothers; hepatic impairment; history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract; inflammatory bowel disease. **Warnings and precautions:** If used in combination with beta-blocking drugs and other antihypertensives, a possible additive effect resulting in postural hypotension should be borne in mind. Adalat LA will not prevent possible rebound effects after cessation of other antihypertensive therapy. Caution in patients whose cardiac reserve is poor. If ischaemic pain is observed following the introduction of therapy, discontinue treatment. Diabetic patients may require adjustment of their control. **Interactions:** Interactions have been observed with cimetidine and quinidine. **Side-effects:** Headache, dizziness, flushing and gravitational oedema. Less common side-effects include rash, nausea, lethargy and increased frequency of micturition, hypersensitivity-type jaundice, and gingival hyperplasia which may regress on withdrawal of therapy. **Legal category:** POM **Package Quantities and Basic NHS Cost:** Calendar packs containing 28 tablets; Adalat LA 30 £11.76, Adalat LA 60 £15.40. **Product Licence Numbers :** PL 0010/0174-0175 **Date of Preparation:** April 1992.

References: 1. Chung M *et al. Hosp Formul* 1990; **25** (Suppl A): 15-19. **2.** Cruickshank J M & McCainsh J. *Acta Therapeutica* 1992; **18:** 53-59. **3.** Data on file.

Further information available from: Bayer UK Limited, Pharmaceutical Business Group, Bayer House, Strawberry Hill, Newbury, Berkshire RG13 1JA. Telephone: (0635) 39000. ® Registered trademark of Bayer AG. © Bayer UK Limited, April 1992. Bayer and ⊕ are trademarks of Bayer AG.

Bayer

Br Heart J 1992;68:253–4

BRITISH
HEART
JOURNAL

Editorial

Graft vascular disease in heart transplant patients

Heart transplantation has become an accepted treatment for end-stage heart failure. According to the Registry of the International Society for Heart Transplantation 2437 heart transplants were performed in 1990.[1] Of these, 98% were orthotopic. Survival rates have improved significantly in recent years, reaching 72% at five years. Operative mortality remains at 10% and is mainly the result of technical complications and right-sided heart failure. Late mortality during the first year is related to infection and rejection in more than 70% of cases.[1] However, after the first year the main cause of morbidity and mortality is graft vascular disease, which has also become the main reason for retransplantation.

Several clinical studies have tried to find prognostic factors for the development of graft vascular disease. Among the factors studied are the type of drugs used for the immunosuppressive treatment (azathioprine *v* cyclosporin),[2] the age of the donor,[3] a previous history of ischaemic heart disease in the recipient,[4] high fasting concentrations of plasma triglycerides,[3] plasma total cholesterol concentration,[4] the number of rejection episodes,[5] the number of untreated rejection episodes,[6] the presence of systemic hypertension,[4 7] diabetes mellitus,[4 7] cytomegalovirus infection[6 8] and HLA mismatch.[4 6] Unfortunately, none of these studies was capable of reliably demonstrating a strong relation between the factors tested and the presence of graft vascular disease.

Graft vascular disease has been angiographically diagnosed five years after transplant in up to 50% of patients,[9] and its frequency is the same in children and in adults. The angiographic appearance of graft vascular disease has been well established:[10] the epicardial coronary arteries are diffusely involved and show concentric narrowing of the lumen. Distal vessel involvement is a prominent feature, which can appear either as gradual tapering or as obliteration ("pruning"). Collateral circulation is generally very poor. A few patients will have angiographic lesions morphologically similar to those seen in native coronary artery disease. The diffuse involvement of the coronary tree together with its mild angiographic appearance make angiographic diagnosis of graft vascular disease quite difficult, even with a trained eye. Coronary angiography remains the most widely used diagnostic tool. The non-invasive techniques such as exercise stress testing and thallium radionuclide angiography have a sensitivity below 50%.[11]

Graft vascular disease differs histologically from native coronary atheroma.[12] The internal elastic lamina and the media are generally spared. Intimal proliferation is concentric and significantly reduces the lumen of the involved artery. This intimal growth is composed of smooth muscle cells, loose collagen, and some foam cells: but no "lipid pool" is seen. In early lesions T lymphocytes predominate but they decrease with time. Calcification and thrombosis are rare, although they can be seen—mostly in the coronary arteries of patients given a heart transplant more than 10 years ago.[13] Small intramyocardial vessels can also be obliterated by the same type of intimal growth.

The aetiology of graft vascular disease is still a matter of debate. The initial vascular lesion has been called an "intimitis"[9] or an "endothelialitis"[14] but its origin and pathogenesis remain to be determined. The hypothesis that the endothelium is damaged during the harvesting of the donor's heart and probably during the preservation period is attractive but unconfirmed. According to this hypothesis, endothelial injury together with platelet aggregation leads to the release of smooth muscle cell mitogens such as endothelium-derived relaxing factor (EDRF) and platelet-derived growth factor (PDGF)[15] that induce smooth muscle cell proliferation. How this proliferation process can so quickly lead to occlusion of the vessel is not known.

Another hypothesis is that of endothelial damage mediated by activated T cells. Recent studies[16] have shown that lymphocyte proliferation induced by interleukin-2 is related to a higher frequency of graft vascular disease. Vascular rejection with morphological demonstration of perivascular immunoglobulin and complement deposits has also been correlated, although only as a statistical trend, with the development of graft vascular disease.[17] Immunohistochemical studies with specific monoclonal antibodies[18] showed cytotoxic T lymphocytes (CD8+) and macrophages in the coronary arteries of patients with graft vascular disease. Both types of cells are known to produce growth factors that can induce smooth muscle cell proliferation. Other workers[19] reported HLA-DR expression on the endothelial cells of hearts with graft vascular disease. HLA-DR positive cells could lead to stimulation of macrophages to produce growth factors such as interleukin-1 and PDGF and thus stimulate smooth muscle cell growth. Clinically, endothelial dysfunction has been shown in small numbers of patients with transplants[20] by acetylcholine-induced vasoconstriction and its lack of reversibility after nifedipine infusion.

In summary, graft vascular disease remains a major long-term cause of morbidity in patients with heart transplants. Retransplantation seems to be the only treatment because percutaneous coronary angioplasty[21] and coronary artery bypass surgery do not produce long-term improvement. The results of retransplantation, however, are poor; graft vascular disease developed in up to 50% of patients at one year.[22] Thus, graft vascular disease remains one of the major obstacles to an improvement in the long-term survival of heart transplant patients.

JESSICA MANN

Department of Cardiological Sciences,
St George's Hospital Medical School,
Cranmer Terrace,
Tooting,
London SW17 0RE.

1 Kriett JM, Kaye MP. The Registry of the International Society for Heart Transplantation: Seventh Official Report—1990. *J Heart Transpl* 1990; **9**:323–30.

2 Gao S, Schroeder JS, Alderman EL, Hunt SA, Valantine HA, Wiederhold V, Stinson EB. Prevalence of accelerated coronary artery disease in heart transplant survivors—Comparison of cyclosporine and azathioprine regimens. *Circulation* 1989;**80**(suppl III):100–5.

3 Gao S, Schroeder JS, Alderman EL, Hunt SA, Silverman JF, Wiederhold V, Stinson EB. Clinical and laboratory correlates of accelerated coronary artery disease in the cardiac transplant patient. *Circulation* 1987;**76**(suppl V):56–61.

4 Olivari MT, Homans DC, Wilson RF, Kubo SH, Ring WS. Coronary artery disease in cardiac transplant patients receiving triple-drug immunosuppressive therapy. *Circulation* 1989;**80**(suppl III):111–5.

5 Uretsky BF, Murali S, Reddy PS, Rabin B, Lee A, Griffith BP, *et al.* Development of coronary artery disease in cardiac transplant patients receiving immunosuppressive therapy with cyclosporine and prednisone. *Circulation* 1987;**76**:827–34.

6 Stovin PGI, Sharples L, Hutter JA, Wallwork J, English TAH. Some prognostic factors for the development of transplant-related coronary artery disease in human cardiac allografts. *J Heart Lung Transplant* 1991;**10**:38–44.

7 Eich D, Thompson JA, Ko D, Hastillo A, Lower R, Katz S, *et al.* Hypercholesterolemia in long-term survivors of heart transplantation: An early marker of accelerated coronary artery disease. *J Heart Lung Transplant* 1991;**10**:45–9.

8 McDonald K, Rector TS, Braunlin EA, Kubo SH, Olivari MT. Association of coronary artery disease in cardiac transplant recipients with cytomegalovirus infection. *Am J Cardiol* 1989;**64**:359–62.

9 Miller LW. Long-term complications of cardiac transplantation. *Prog Cardiovasc Dis* 1991;**33**:229–82.

10 Gao S, Alderman EL, Schroeder JS, Silverman JF, Hunt SA. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. *J Am Coll Cardiol* 1988;**12**:334–40.

11 Smart FW, Ballantyne CM, Cocanougher B, Farmer JA, Sekela ME, Noon GP, Young JB. Insensitivity of noninvasive tests to detect coronary artery vasculopathy after heart transplant. *Am J Cardiol* 1991;**67**:243–7.

12 Billingham ME. The postsurgical heart—The pathology of cardiac transplantation. *Am J Cardiovasc Pathol* 1988;**1**:319–34.

13 Uys CJ, Rose AG. Pathologic findings in long-term cardiac transplants. *Arch Pathol Lab Med* 1984;**108**:112–6.

14 Hruban RH, Beschorner WE, Baumgartner WA, Augustine SM, Ren H, Reitz BA, Hutchins GM. Accelerated arteriosclerosis in heart transplant recipients is associated with a T-lymphocyte-mediated endothelialitis. *Am J Pathol* 1990;**137**:871–82.

15 Ip JH, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: Role of vascular injury and smooth muscle cell proliferation. *J Am Coll Cardiol* 1990;**15**:1667–87.

16 Kaufman C, Zeevi A, Zerbe T, Keenan R, Kormos R, Griffith B, *et al.* In vitro culture of infiltrating lymphocytes from coronary arteries and endomyocardial biopsies: Association with graft coronary disease. *Transplant Proc* 1991;**23**:1142–3.

17 Ensley RD, Hammond EH, Renlund DG, Yowell RL, Bristow MR, DeWitt CW, *et al.* Clinical manifestations of vascular rejection in cardiac transplantation. *Transplant Proc* 1991;**23**:1130–2.

18 Hruban RH, Beschorner WE, Baumgartner WA, Augustine SM, Reitz BA, Hutchins GM. Accelerated arteriosclerosis in heart transplant recipients: An immunopathology study of 22 transplanted hearts. *Transplant Proc* 1991;**23**:1230–2.

19 Salomon RN, Hughes CCW, Schoen FJ, Payne DD, Pober JS, Libby P. Human coronary transplantation-associated arteriosclerosis. *Am J Pathol* 1991;**138**:791–8.

20 Nellessen U, Lee TC, Fischell TA, Ginsburg R, Masuyama T, Alderman EL, *et al.* Effects of acetylcholine on epicardial coronary arteries after cardiac transplant without angiographic evidence of fixed graft narrowing. *Am J Cardiol* 1988;**62**:1093–7.

21 Halle AA, Wilson RF, Vetrovec GW. Applications of percutaneous transluminal coronary angioplasty in cardiac transplantation. Preliminary results in five patients. *Circulation* 1988;**78**(suppl III):83–6.

22 Gao SZ, Schroeder JS, Hunt S, Stinson EB. Retransplantation for severe accelerated coronary artery disease in heart transplant recipients. *Am J Cardiol* 1988;**62**:876–81.

Br Heart J 1992,**68**:255–6

Editorial

Coronary artery disease after heart transplantation: clinical aspects

Occlusive coronary artery disease is now the main complication limiting long-term survival after heart transplantation[1–3] and also the most common indication for retransplantation.[1] The reported angiographic prevalence ranges from 2% to 28% one year after transplantation,[4,5] increasing to 40–70% by five years.[6–8] Most of these patients, however, have only minor coronary stenoses or minimal luminal irregularities.[8,9] There are as yet few data available about the rate of progression and clinical significance of these minor changes. In this issue (pages 260–5) Mullins *et al* report a three year survival of 60–80% after first diagnosis of coronary disease, which depends on the number of vessels involved.[8] When the disease is more advanced survival rates are poor. Keogh *et al*[10] report actuarial three year survival rates of 6% and 22% for advanced (⩾40% stenoses) triple and single vessel disease respectively.

The clinical presentation of occlusive coronary disease in transplant recipients is very different from that in other patients. The importance of relatively minor coronary occlusive disease can be substantially increased by a tendency to increased platelet aggregation[11] and blood hypercoagulability caused by high serum concentrations of fibrinogen and factors VIIC and VIIIC.[12] Although a few transplant patients probably do experience angina[13] most will have silent ischaemia because of autonomic denervation after surgery. As with conventional coronary disease, advanced disease in the transplanted heart is associated with frequent multifocal and complex ventricular activity and sudden death.[14] Progressive heart failure caused by recurrent infarction or progressive ischaemia can develop. Acute myocardial infarction in transplant recipients is usually painless although they may report dyspnoea, palpitation or sudden weakness.[15] The electrocardiographic changes may be slight because of the diffuse and atypical pattern of infarction.[15]

Because there is no effective treatment for established coronary occlusive disease in transplant recipients prevention is an important priority. Existing studies have been retrospective and have used widely differing diagnostic criteria. They have produced few data that are directly applicable to the management of patients being given transplants today.

Effective future research will require the best methods of diagnosis and assessment of transplant related coronary disease. Existing studies have relied heavily on conventional coronary arteriography which has very serious limitations. It consistently underdiagnoses coronary disease in transplant recipients and underestimates its severity.[6,9,16] Quantitative angiography has improved sensitivity particularly in detecting smooth concentric vessel narrowing.[16] Intracoronary ultrasound also enables more accurate assessment of smooth concentric stenoses but the size of the probe restricts its use to large epicardial vessels.[17] The widespread involvement of small vessels in transplant related coronary occlusive disease[18] probably limits the usefulness of these methods of assessment that are solely anatomical.

Functional assessment by non-invasive techniques has proved disappointing with too low a sensitivity for routine use.[19] Intracoronary Doppler measurement of blood flow can be readily combined with conventional angiography and this approach may provide a more comprehensive evaluation of the occlusive disease.[20]

Although there are few good data on which to base recommendations about patient management it seems prudent to treat hypertension vigorously, to advise patients to eat a diet low in saturated fat, and to avoid cigarette smoking and excessive weight gain. Despite these measures many recipients will continue to have "atherogenic" lipid profiles,[21] and this raises the question of drug treatment for hyperlipidaemia. Unfortunately, when the very effective hydroxymethylglutaryl co-enzyme A reductase inhibitors are used in combination with cyclosporin they can occasionally cause rhabdomyolysis and renal failure and therefore may be too hazardous to be recommended for widespread use.[22] The effectiveness of aspirin in other patients may encourage its use in established coronary disease but it is probably not widely appreciated that its effectiveness is seriously limited by changes in platelet aggregation in transplant patients.[11]

Some centres have advocated steroid-free maintenance immunosuppression[23] to reduce coronary disease. It may be particularly effective in children[24] and is also desirable for their optimum growth. In adults, however, its effectiveness is unproven, and given the suspected immunological nature of the process this approach may be deleterious. The preliminary results of a randomised trial of diltiazem in the prevention of graft coronary disease from the Stanford group[25] are encouraging but further data are needed before it can be recommended for routine practice. In animal models low molecular weight heparin, which reduces smooth muscle cell proliferation, has been shown to reduce the severity of occlusive disease.[26]

What are now required are large scale, multicentre, randomised, prospective trials of management strategies with clearly defined end points. Advanced assessment techniques such as those discussed would be preferable. Intensive drug treatment of hyperlipidaemia, steroid-free maintenance immunosuppression, and the prophylactic use of calcium antagonists or low molecular weight heparin would be suitable for this type of study. The role of cardiac autograft rejection also needs to be investigated further particularly with reference to the question of maintenance steroid therapy. Because the United Kingdom has a relatively small number of centres, each performing substantial numbers of transplants, we are in an ideal administrative position to undertake such studies.

CHRISTOPHER D SCOTT
JOHN H DARK

Freeman Hospital,
Newcastle upon Tyne

1 Kriett JM, Kaye MP The Registry of the International Society for Heart and Lung Transplantation Eighth Official Report, 1991 *J Heart Lung Transplant* 1991;10:491–8.
2 Billingham ME Graft coronary disease: the lesions and the patients *Transplant Proc* 1989,21·3665–6
3 Bieber CP, Hunt SA, Schwinn DA, *et al.* Complications in long term survivors of cardiac transplantation *Transplant Proc* 1981,13.207–11

4 O'Neill BJ, Pflugfelder PW, Singh NR, *et al.* Frequency of angiographic detection and quantitative assessment of coronary arterial disease one and three years after cardiac transplantation. *Am J Cardiol* 1989,63:1221–5.

5 Balk AHMM, Linden MVD, Meeter K, *et al.* Is there a relation between transplant coronary artery disease and the occurrence of CMV infection? [Abstract] *J Heart Lung Transplant* 1991;10.188.

6 Gao SZ, Schroeder JS, Alderman EL, *et al.* Prevalence of accelerated coronary artery disease in heart transplant survivors. *Circulation* 1989,80(suppl III):100–5.

7 Narrod J, Kormos R, Armitage J, *et al.* Acute rejection and coronary artery disease in long term survivors of heart transplantation. *J Heart Lung Transplant* 1989;8:418–20

8 Mullins PA, Cary N, Sharples L, *et al* Coronary occlusive disease and late graft failure after cardiac transplantation. *Br Heart J* 1992,68:260–5.

9 Uretsky BF, Murali S, Reddy S, *et al.* Development of coronary artery disease in cardiac transplant patients receiving immunosuppressive therapy with cyclosporine and prednisone. *Circulation* 1987;76:827–34.

10 Keogh A, Valantine H, Hunt S, *et al.* Impact of transplant coronary artery disease on survival after cardiac transplantation [Abstract]. *J Heart Lung Transplant* 1991,10:172.

11 de Lorgeril M, Dureau G, Boissonnat P, *et al* Increased platelet aggregation after heart transplantation· influence of aspirin. *J Heart Lung Transplant* 1991;10:600–3.

12 Hunt BJ, Segal H, Yacoub M. Haemostatic changes after heart transplantation and their relationship to accelerated coronary sclerosis *Transplant Proc* 1991,23 1233–5.

13 Schroeder JS, Hunt SA. Chest pain in heart transplant patients *N Engl J Med* 1991,324.1805–6.

14 Romhilt DW, Doyle M, Sagar KB, *et al.* Prevalence and significance of arrhythmias in long-term survivors of cardiac transplantation. *Circulation* 1982,66(suppl I):219–22.

15 Gao SZ, Schroeder JS, Hunt SA, *et al.* Acute myocardial infarction in cardiac transplant recipients. *Am J Cardiol* 1989;64:1093–7

16 Gao SZ, Alderman EL, Schroeder JS, *et al.* Progressive coronary luminal narrowing after cardiac transplantation. *Circulation* 1990;82(suppl IV):269–75.

17 Pinto FJ, StGoar FG, Alderman EL, *et al.* Intracoronary ultrasound evaluation of coronary artery disease in cardiac transplant recipients: a new "gold standard"? [Abstract]. Proceedings of European Society for Organ Transplantation 1991.141.

18 Gao SZ, Alderman AL, Schroeder JS, Silverman JF, Hunt SA. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings *J Am Coll Cardiol* 1988;12.334–40.

19 Smart FW, Ballantyne CM, Cocanougher B, *et al.* Insensitivity of noninvasive tests to detect coronary artery vasculopathy after heart transplantation *Am J Cardiol* 1991;67:243–7.

20 Mullins P, Scott J, Aravot D, *et al.* Small vessel coronary occlusive disease after cardiac transplantation [Abstract] *J Am Coll Cardiol* 1991;17·308.

21 Stamler JS, Vaughan DE, Rudd A, *et al.* Frequency of hypercholesterolaemia after cardiac transplantation. *Am J Cardiol* 1988;62: 1268–72.

22 Corpier CL, Jones PH, Suki WN, *et al.* Rhabdomyolysis and renal injury with lovastatin use. Report of two cases in cardiac transplant recipients. *JAMA* 1988;260·239–41.

23 Ratkovec RM, Wray RB, Renlund DG, *et al.* Influence of corticosteroid-free maintenance immunosuppression on allograft coronary disease after cardiac transplantation. *J Thorac Cardiovasc Surg* 1990,100:6–12.

24 Radley-Smith R, Yacoub M. Low incidence of accelerated coronary sclerosis in children undergoing cardiac transplantation maintained on cyclosporin and azathioprine only [Abstract]. *J Am Coll Cardiol* 1991,17:102.

25 Schroeder JS, Gao SZ, Alderman EL, Hunt SA, Stinson EB Diltiazem inhibits development of early coronary arterial narrowing in cardiac allografts [Abstract]. *J Heart Lung Transplant* 1991,10:173.

26 Aziz S, Tada Y, Verrier E, Fareed J, Gordon D. Reduction in accelerated graft atherosclerosis by low molecular weight heparin plus cyclosporin [Abstract]. *J Heart Lung Transplant* 1992,11:211.

Br Heart J 1992;68:257–9

Editorial

Ventricular remodelling after myocardial infarction

Acute myocardial infarction can cause complex architectural changes in the ventricular myocardium that have an important bearing on ventricular function. In the past decade it has become evident that many patients with acute myocardial infarction undergo these complex changes and that these alterations affect outcome after acute myocardial infarction. Interest is growing in the evaluation of various interventions designed to reduce these changes and so improve left ventricular function and clinical outcome.

Terminology, definitions, and time course

We define ventricular remodelling as changes in shape and size of the left ventricle that can follow acute myocardial infarction. Infarct expansion and global ventricular dilatation are the processes that constitute ventricular remodelling. Infarct expansion, defined as disproportionate thinning and lengthening of the infarct zone resulting in regional distortion and dilatation of the cavity is seen within hours of the injury and is usually complete within three weeks. Global ventricular dilatation is defined as an increase in the overall size and distortion of the ventricular cavity resulting from expansion of the infarct zone and lengthening of the non-infarcted zone. Infarct expansion together with ventricular dilatation and the shape alterations seen up to about six weeks constitute the early remodelling phase and progressive ventricular dilatation seen from six weeks to about one year constitutes the late remodelling phase.[1] During this late phase no important changes are seen in the scarred infarct zone.

Infarct expansion

Microscopically, infarct expansion is caused by myocyte slippage, which thins the infarct segment by reducing the number of cells across the myocardial wall.[2] Grossly, the wall of the infarct zone shows thinning, lengthening, and regional cavity dilatation and bulging (figs 1 and 2).

FACTORS ASSOCIATED WITH INFARCT EXPANSION

Infarct expansion is characteristically seen in anteroapical transmural infarcts and is rare at other sites. Infarct expansion occurs in approximately 40% of anteroapical transmural infarcts and 70% of such infarcts with fatal outcome in the first 30 days.[3 4] Although a critical amount of myocardial necrosis, more than 10%, is necessary to produce infarct expansion, the correlation between infarct size and the presence of expansion is weak. Other factors that promote expansion are increased loading conditions (both preload and afterload), and measures to reduce these have been shown to reduce expansion.[5 6] Expansion is less likely where there is pre-existing hypertrophy,[7] scar tissue from previous ischaemic episodes, and non-transmural infarcts (where a rim of viable epicardium splints the infarct area). Intramyocardial haemorrhage, associated with reperfusion therapy, and its subsequent organisation may alter the tensile strength of the infarct zone to make it more resistant to deforming forces.[8] Administration of steroids and non-steroidal anti-inflammatory agents in the hours and days after myocardial necrosis promotes expansion by reducing the interstitial oedema and cellular infiltration that can provide mechanical support to the myocytes and prevent myocyte slippage.[9–11]

CLINICAL CONSEQUENCES

The increase in functional infarct size and the regional deformation of ventricular cavity shape have implications for left ventricular function and myocardial ischaemia in the non-infarcted, remote myocardium that may be perfused by a critically narrowed coronary vessel: therefore the presence of expansion is associated with reduced exercise tolerance caused by dyspnoea and angina. The presence of expansion is an independent risk factor for the development of left ventricular mural thrombus, frank ventricular aneurysm formation with its attendant complications, and cardiac rupture (both septal and free wall).

Global ventricular dilatation

The reduction in stroke volume and increased left ventricular filling pressure that result from the abrupt loss of segmental contractile function elicit two compensatory mechanisms initially. These are an increase in the contrac-

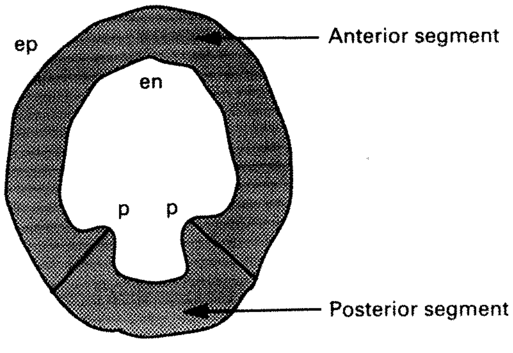


Figure 1 Diagram of a normal cross sectional short axis echocardiogram at mid papillary level showing normal myocardial thickness and cavity shape. p papillary muscles; en, endocardium; ep, epicardium.

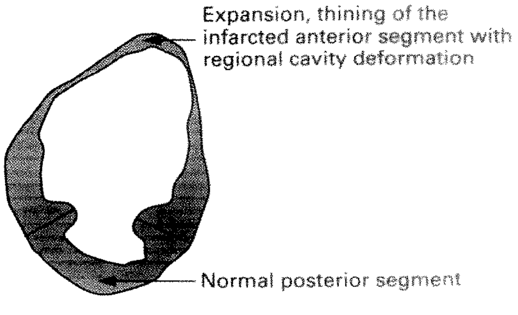

Expansion, thining of the infarcted anterior segment with regional cavity deformation
Normal posterior segment

Figure 2 Diagram of cross sectional short axis echocardiogram at mid-papillary muscle level in anterior myocardial infarction showing infarct expansion.

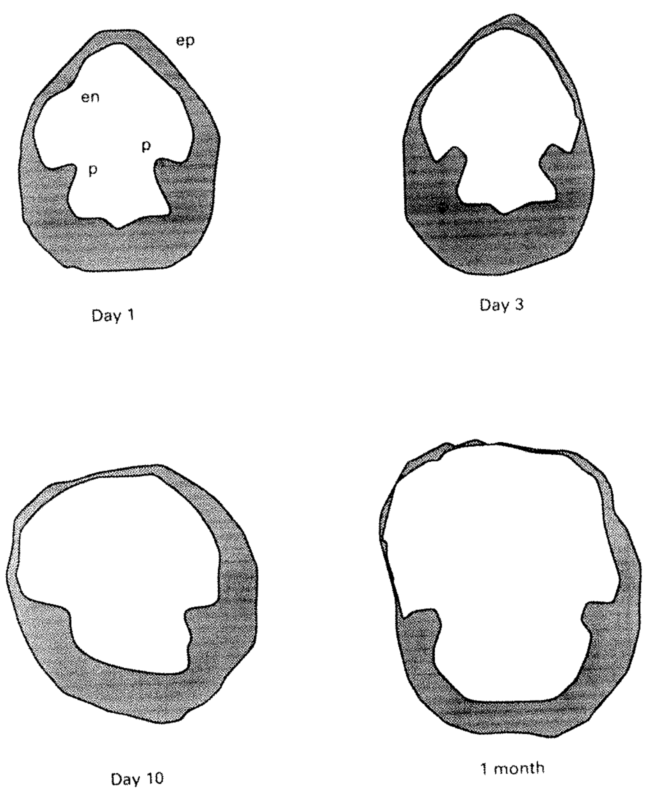


Figure 3 Diagrams of serial cross sectional short axis echocardiogram in anterior myocardial infarction showing infarct expansion (regional thinning and cavity deformation) and global ventricular dilatation (progressive global cavity dilatation and shape distortion). en, endocardium; ep, epicardium; p, papillary muscles.

tility of the viable myocardium stimulated by neurohormonal factors and a rise in end diastolic volume which through the operation of Frank–Starling mechanism serve to normalise filling pressure and restore stroke volume. These changes cause myocyte stretching, an increase in the length of the non-infarcted segment, and cavity dilatation. When the mass of the myocardial necrosis exceeds 20% of the total myocardial mass these two compensatory responses are inadequate to sustain optimal haemodynamic function and the third principal myocardial compensatory reserve, myocardial hypertrophy, is called upon. In patients with myocardial infarction this hypertrophy is the result of the addition of new sarcomeres in series which increases myocyte length and muscle mass without changing muscle thickness. This pattern of hypertrophy, called eccentric hypertrophy, is typical of volume overload states and results in chamber dilatation.

The disproportionate increase in cavity volume in relation to myocardial thickness produces a relative lack of decrease in the internal ventricular radius during ejection and this results in greater wall tension (Laplace's law) that is sustained during systole. This increase in systolic wall stress induces an increase in myocyte volume in the non-infarct zone that is typical of concentric hypertrophy. When these hypertrophic responses match the abnormal loading conditions haemodynamic function and cardiac size may stabilise but in large infarcts the hypertrophic response is inadequate both because of an insufficient increase in ventricular mass over cavity volume and insufficient response in the new capillary network to support the hypertrophy. Thus contractile function is impaired.[12] A vicious circle is established in which abnormal loading conditions elicit an inadequate compensatory response that perpetuates the abnormal loading conditions and promotes progressive ventricular dilatation. Dilatation begets dilatation. In the early remodelling phase, infarct expansion together with changes in the non-infarct segment contribute to global ventricular dilatation whereas in the late remodelling phase ventricular dilatation is almost exclusively caused by changes in the non-infarct segment (fig 3).

FACTORS ASSOCIATED WITH GLOBAL VENTRICULAR DILATATION

Big infarcts,[13] the presence of infarct expansion with the consequent effects of sustained abnormal loading conditions on the non-infarcted myocardium, and persistent occlusion of the infarct related coronary artery are the three important factors that promote progressive ventricular dilatation,[14,15] and the presence of clinically significant stenosis in the non-infarct related coronary artery has an important influence on the compensatory changes seen in the viable myocardium.[16]

CLINICAL CONSEQUENCES

The left ventricular volume is one of the most powerful predictors of mortality after myocardial infarction and progressive ventricular dilatation is a precursor for the development of overt heart failure and is an important prognostic indicator of mortality after myocardial infarction.[17]

Alterations in ventricular shape

Alterations in ventricular shape and ventricular cavity geometry are important consequences of infarct expansion and global ventricular dilatation. Expansion of the necrotic myocardium and consequent regional shape distortion is a reversible elastic process, but after 24 hours plastic changes in the infarct zone result in permanent distortion though infarct expansion can still be reduced after this stage. Global ventricular dilatation results in a more spherical chamber: in general the degree of sphericity of the chamber seems to parallel increases in ventricular volume.

CLINICAL CONSEQUENCES

Preservation of dynamic and static ventricular geometry has implications for ventricular function[18] and though the static geometry of the chamber seems to be related to the volume of the chamber it is tempting to suggest that the dynamic geometry of the dilated chamber and hence the function of the chamber may be independent of ventricular volume.

Pharmacological interventions

Reperfusion treatment with thrombolytic agents, early and late, is the most important pharmacological intervention that prevents infarct expansion in the early period after myocardial infarction. Early reperfusion therapy limits expansion by myocardial salvage while late reperfusion reduces expanion independently of myocardial salvage by limiting transmural damage and opening up collateral blood flow to the infarct zone thereby preserving a rim of viable epicardium.[8,19] Infarct expansion may also be limited by unloading agents such as intravenous glyceryl trinitrate[20] and intravenous calcium channel blockers.[21] It is conceivable that intravenous β blockers, by reducing sympathetic activity and afterload, reduce the deforming forces acting on the infarct area and hence prevent expansion and cardiac rupture.[22]

Limitation of infarct size by reperfusion therapy and measures to reduce infarct expansion are the important interventions in the early hours after myocardial infarction that reduce global ventricular dilatation. Though persistent occlusion of the infarct related coronary artery and critical narrowing in the coronary vessels supplying the non-infarcted myocardium have an important bearing on global ventricular dilatation, the best method of achieving optimum coronary artery patency is still not clear.

There is evidence that ventricular unloading therapy in the first 24 hours with intravenous glyceryl trinitrate reverses the distortion of the cavity associated with infarct expansion and although reperfusion therapy also serves to preserve the regional shape the mechanism is one of myocardial salvage.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

Recently the role of ACE inhibitors in the attenuation of ventricular remodelling has been increasingly explored and these are clearly an exciting class of agents. ACE inhibitors by reducing loading conditions and altering the neurohormonal response to myocardial infarction have been shown, experimentally, to reduce infarct expansion; some preliminary studies in patients treated with ACE inhibitors within few hours of infarction seem to confirm this.[23–25] Certainly, we did not experience any important management problems when we used intravenous enalaprilat and oral enalapril within 24 hours of infarction in addition to streptokinase and intravenous glyceryl trinitrate.

There is now ample experimental and clinical evidence that the use of ACE inhibitors after infarct expansion has occurred or even in the late remodelling phase reduces global ventricular dilatation by optimising ventricular loading conditions and wall stress,[26 27] and possibly through alterations in the myofibre structure and protein and collagen content.[28] Perhaps more exciting is the evidence that administration of ACE inhibitors a year after myocardial infarction resulted in partial reversal of left ventricular dysfunction.[29]

Experimental evidence indicates that ventricular unloading by use of ACE inhibitors in the first 24 hours reverses the regional shape distortion and that continued use of these agents in the recovery phase serves to preserve ventricular shape and internal geometry.

Methods to study ventricular remodelling

Methods available to study ventricular remodelling include cross sectional echocardiography, computed tomography, magnetic resonance imaging, radionuclide ventriculography, and contrast ventriculography. Cross sectional echocardiography, in view of its ease of performance of serial studies both in the early and follow up period, sophistication, and cost, provides the best practical way to study ventricular remodelling. The limitations of this technology are that in some patients the quality of the images may be unsatisfactory and direct visualisation of coronary anatomy impossible. The other non-invasive techniques of computed tomography and magnetic resonance imaging provide high quality tomographic images that are not limited by patient factors, although the high cost and the relative immobility of the equipment makes serial studies in the acute phase difficult. Alterations in ventricular volume and shape may be estimated by radioisotope ventriculography and contrast ventriculography and information about coronary anatomy may be obtained from coronary arteriography.

Future directions

Although currently available information suggests that the patient with a large, first, anteroapical myocardial infarction is at the greatest risk of ventricular remodelling, more information is required to assess the risk in different subgroups by means of a simple non-invasive test. Whereas reperfusion therapy with thrombolytic agents and unloading therapy by intravenous nitrates help to counteract remodelling the use of calcium channel blockers and β blockers needs further clarification. The use of ACE inhibitors holds great promise and trials that are underway should further clarify the role of these agents. More research is also essential in defining the optimal combination of these various agents with reperfusion therapy and the timing of the start of therapy and duration of therapy that gives the best results.

MANI A VANNAN
DERYCK J E TAYLOR

*Cardiac Department,
Kent and Canterbury Hospital,
Canterbury CT1 3NG.*

1 Erlebacher JA, Weiss JL, Weisfeldt ML, Bulkley BH Early dilation of the infarcted segment in acute transmural myocardial infarction Role of infarct expansion in acute left ventricular enlargement *J Am Coll Cardiol* 1984,4:201–8

2 Weisman HF, Bush DE, Mannisi JA, Weisfeldt ML, Healy B. Cellular mechanisms of myocardial infarct expansion *Circulation* 1988,78 186–201

3 Pirolo JS, Hutchins GM, Moore GW Infarct Expansion: Pathologic analysis of 204 patients with a single myocardial infarct *J Am Coll Cardiol* 1986,7 349–54

4 Weisman HF, Healy B Myocardial infarct expansion, infarct extension and reinfarction· Pathophysiologic concepts. *Prog Cardiovasc Dis* 1987,30 73–110.

5 Nolan SE, Mannisi JA, Bush DE, Healy B, Weisman HF Increased afterload aggravates infarct expansion after myocardial infarction *J Am Coll Cardiol* 1988,12.1318–25

6 Pierard LA, Albert A, Gilis F, Sprynger M, Carlier J, Kulbertus HE Haemodynamic profile of patients with acute myocardial infarction at risk of infarct expansion *Am J Cardiol* 1987;60 5–9

7 Weisman HF, Udvarhelyi S, Bush DE, *et al* Inducing hypertrophic shape changes in noninfarcted myocardium prevents progresssion of infarct expansion [abstract]. *Clin Res* 1984;32 216.

8 Hale SL, Kloner RA. Left ventricular topographical alterations in the completely healed rat infarct caused by early and late coronary artery reperfusion. *Am Heart J* 1988,116 6:1508–13

9 Mannisi JA, Weisman HF, Bush DE, Dudeck P, Healy B Steroid administration after myocardial infarction promotes early infarct expansion. *J Clin Invest* 1987,79.1431–39

10 Jugdutt BI Delayed effects of early infarct-limiting therapies on healing after myocardial infarction *Circulation* 1985,72·907–14

11 Hammerman H, Schoen FJ, Braunwald E, Kloner RA Drug induced expansion of infarct Morphologic and functional correlations. *Circulation* 1984,69.611–7

12 Anversa P, Beghi C, Kikkawa Y, Olivetti G Myocardial infarction in rats. Infarct size, myocyte hypertrophy and capillary growth *Circulation Res* 1986,58 26–37.

13 Kitamura S, Kay JH, Krohn BG, Magidson O, Dunne EF Geometric and functional abnormalities of the left ventricle with a chronic localized noncontractile area. *Am J Cardiol* 1973,31.701–7

14 Jeremy RW, Hackworthy RA, Bautovich G, Hutton BF, Harris PJ Infarct artery perfusion and changes in left ventricular volume in the month after acute myocardial infarction *J Am Coll Cardiol* 1987,9 989–95

15 Leung W-H, Lau C-P. Effects of severity of residual stenosis of the infarct related coronary artery on left ventricular remodelling and function after myocardial infarction [abstract] *Circulation* 1991,84(suppl II) 476

16 Kalil R, Albuquerque C, Caramelli G, *et al*. Late function in the remote region following myocardial infarction The importance of stenosis in the non-infarct related artery [abstract]. *Circulation* 1991,84(suppl II) 476

17 Jeremy RW, Allman KC, Bautovich G, Harris PJ. Patterns of left ventricular dilatation during the six months after myocardial infarction *J Am Coll Cardiol* 1989;13 304–10

18 Kass DA, Traill TA, Keating M, Altieri PI, Maughan WL Abnormalities of dynamic ventricular shape change in patients with aortic and mitral valvular regurgitation. Assessment by fourier shape analysis and global geometric indexes. *Circulation Res* 1988,62:127–38.

19 Hochman JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. *Circulation* 1987,75 299–306

20 Jugdutt BI, Warnica JW Intravenous nitroglycerine therapy to limit myocardial infarct size, expansion and complications Effect of timing, dosage and infarct location *Circulation* 1988,78 906–19

21 Gottlieb SO, Gerstenblith G, Shapiro EP, *et al*. Nifedipine reduces early infarct expansion results of a double-blind, randomised trial [abstract]. *Circulation* 1985,72(suppl III):274

22 ISIS-1 Collaborative Group Mechanisms for the early mortality reduction produced by beta blockade started early in acute myocardial infarction *Lancet* 1988,i·921–3

23 Nabel EG, Topol EJ, Galeana A, *et al* A randomized, double-blind, placebo controlled, pilot trial of combined early intravenous captopril and tPA therapy in acute myocardial infarction [abstract] *Circulation* 1989,80 (suppl II) 112.

24 Sharpe N, Smith H, Murphy J, Greaves S, Hart H, Gamble G Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. *Lancet* 1991,337 872–6

25 Pye M, Oldroyd KG, Ray SG, Christie J, *et al* Effects of early captopril administration on left ventricular dilatation and function after acute myocardial infarction [abstract] *Circulation* 1990,82(suppl III) 674.

26 Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chroic captopril therapy on the infarcted left ventricle of the rat. *Circulation Res* 1985,57 84–95

27 Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction *N Engl J Med* 1988,319:80–6.

28 Michel JB, Lattion AL, Salzman JL, *et al* Hormonal and cardiac effects of converting enzyme inhibition in rat myocardial infarction *Clin Res* 1988; 62:641–50

29 Sharpe N, Smith H, Murphy J Late reversal of left ventricular dysfunction following myocardial infarction [abstract] *Circulation* 1989;80(suppl II):253

Br Heart J 1992;68:260–5

Coronary occlusive disease and late graft failure after cardiac transplantation

P A Mullins, N R Cary, L Sharples, J Scott, D Aravot, S R Large, J Wallwork, P M Schofield

Transplant Unit, Papworth Hospital, Papworth Everard, Huntingdon, Cambridge
P A Mullins
N R Cary
L Sharples
J Scott
D Aravot
S R Large
J Wallwork
P M Schofield

Correspondence to:
Dr P Mullins, Transplant Unit, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE.

Accepted for publication 1 May 1992

Abstract

Objective—Coronary occlusive disease is the main cause of late mortality after cardiac transplantation. It has both similarities and differences compared with conventional atherosclerotic coronary disease. The pathophysiology of late graft failure from coronary occlusive disease is unclear at present. We reviewed the experience of this disorder in our cardiac transplant programme.

Design—A retrospective analysis of angiographic and pathological data.

Setting—A regional cardiothoracic centre and transplant unit.

Patients—Of a population of 383 orthotopic cardiac transplant recipients operated upon between January 1979 and June 1990, 447 coronary angiograms were available for review in 193 patients. Thirteen of a possible 18 results of post mortem examinations from patients dying from coronary occlusive disease were available.

Main outcome measure—Coronary occlusive disease was defined as any evidence of disease on coronary angiography. Post mortem examinations were performed with standard techniques.

Results The angiographic prevalence of coronary occlusive disease was 3% (1/32 patients) and 40% (19/47 patients) at one and five years respectively. Twenty six grafts failed due to coronary occlusive disease compared with 132 graft failures from all causes during this period. Acute thrombosis was present in a large vessel in seven of 13 fatal cases undergoing necropsy (54%). Noticeable large vessel involvement with disease in smaller distal vessels was present in four patients (31%). The remaining two patients (15%) had small vessel disease alone. Twelve of the 13 patients had significant cardiomegaly (cardiac weight ⩾400 g) with a mean weight of 510 (range 370–740) g.

Conclusion—Coronary occlusive disease is the main late complication after cardiac transplantation. A combination of coronary thrombosis, ischaemia from stenoses of large and small coronary vessels, and cardiomegaly contribute to the graft failure of these patients.

(Br Heart J 1992;68:260–5)

Coronary occlusive disease is the main cause of death in orthotopic cardiac transplant recipients more than one year after cardiac transplantation.[1] This disease differs from conventional atherosclerosis in that it is tubular, concentric, diffuse, and often affects smaller coronary vessels.[2 3] It may not only develop proximally in larger coronary arteries as in conventional atherosclerosis, but may be distal and obliterative (fig 1). Often it appears as a combination of these types of lesion and characteristically progresses rapidly.[4] As patients are denervated at the time of operation, cardiac ischaemia can develop without symptoms until severe cardiac dysfunction and death occurs.[5]

Serial coronary angiography has been the main method of assessing coronary occlusive disease after operation. It is performed to detect coronary disease and left ventricular dysfunction, and to plan appropriate treatment. Also it is used as a research tool for studying a form of accelerated coronary disease in humans. What remains unclear is the prognostic importance of the various coronary angiographic lesions found in patients with coronary occlusive disease, and what is the mechanism of graft failure and death.

We documented the incidence and time to occurrence of any form of coronary occlusive disease as apparent from coronary angiography at our hospital. We reviewed the available data from post mortem examination

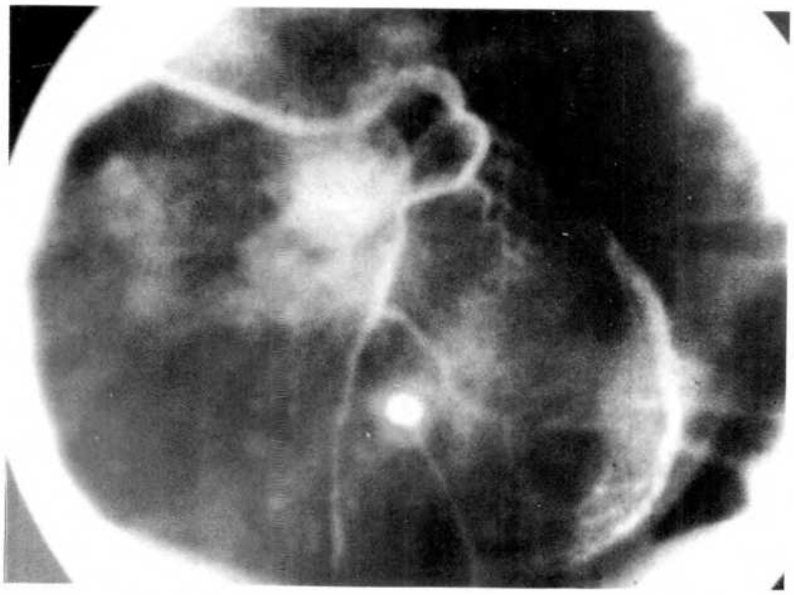


Figure 1 Left anterior oblique view showing diffuse irregularity and terminal occlusion of left anterior descending and left circumflex coronary artery.

of patients who died during the study, and examined some of the processes which led to graft failure.

Patients and methods

A total of 383 patients received their first cardiac transplant at Papworth Hospital between January 1979 and June 1990. Most (88%) of the recipients were male (n = 338). The mean age of these patients was 44 (range 6–63) years at the time of operation. Ischaemic heart disease (53%) and dilated cardiomyopathy (43%) were the main indications for transplantation.

IMMUNOSUPPRESSIVE TREATMENT

The first 29 patients in the cardiac transplant programme received azathioprine and prednisolone only. Cyclosporin was introduced at Papworth Hospital in March 1982 and was used in 121 patients in conjunction with either azathioprine or prednisolone for the next four years (double treatment). Triple treatment, combining cyclosporin with azathioprine and prednisolone, was started in April 1986. Oral steroids are gradually withdrawn, if possible, in the triple treatment group starting three months after operation.

ANGIOGRAPHY PROTOCOL

Up to March 1983, patients underwent annual coronary angiography. After this time, a different protocol was devised. The first coronary angiogram is now performed two years after operation. If coronary occlusive disease is detected, annual angiography is performed and if not, the next angiogram is performed at four years. After four years, all patients undergo annual angiography.

Angiograms were assessed serially for each patient by two observers blinded to the clinical history. Coronary occlusive disease was defined as any sign of disease on angiography. Coronary disease was graded according to the diameter of the stenosis of the most severe lesion compared with an adjacent healthy artery. The primary coronary arteries were defined as the left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery. Their main branches were classified as secondary coronary arteries (first and second diagonal, first and second obtuse marginal, and posterolateral or posterior descending branch of the right coronary artery). Initially, attempts to assess disease angiographically in smaller (tertiary) branches of these arteries were made. Without annual serial films, the consistent ability to detect disease affecting these vessels in all patients was not possible.[4] Therefore this approach was abandoned. Significant coronary disease was defined as a lesion producing a greater than 50% reduction in intraluminal arterial diameter.

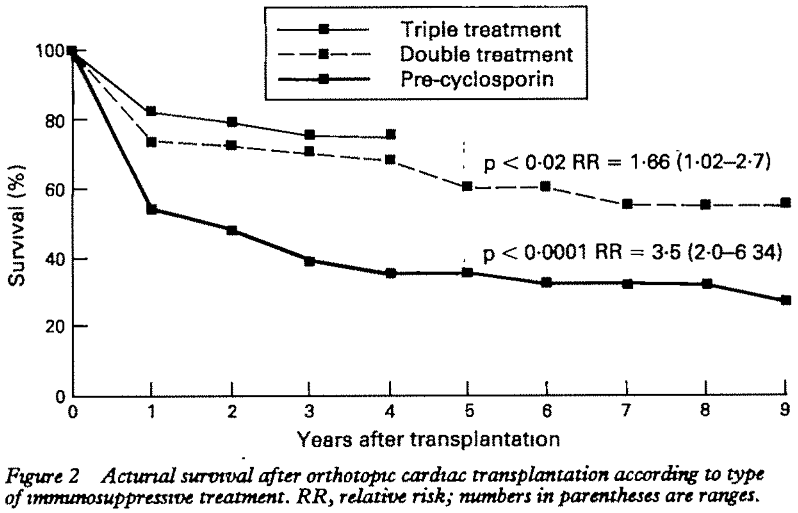


Figure 2 Actuarial survival after orthotopic cardiac transplantation according to type of immunosuppressive treatment. RR, relative risk; numbers in parentheses are ranges.

PATHOLOGY

Efforts to procure the heart for pathological examination were made in all patients who died. After fixation in buffered formalin solution, the coronary arteries were examined throughout their lengths. Serial transverse sections were taken at regular intervals and paraffin sections were stained with haematoxylin and eosin. Both large (primary and secondary) and small (tertiary) vessels were examined by light microscopy. Cardiomegaly was defined as a post mortem heart weight of ≥400 g.[6] The diagnosis of death due to coronary occlusive disease was made in several patients at post mortem examinations performed at other hospitals. Unless the heart was released for examination here, this data is not included in our study.

STATISTICAL METHODS

Statistical analysis was performed with the *BMDP* statistics package. Results are expressed as mean (ranges) for continuous measurements. Actuarial survival was calculated by the life table method. The risk of death associated with improved immunosuppressive treatment was assessed by Cox regression analysis and tested with the likelihood ratio test.

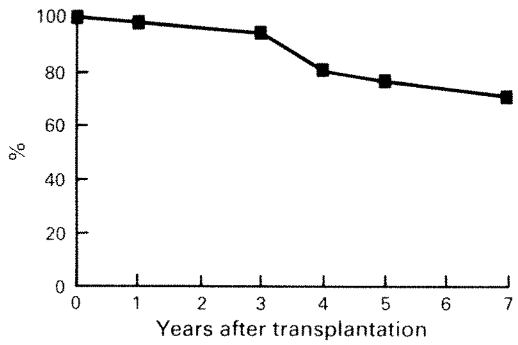
Results

The overall survival figures have improved with changes in immunosuppressive treatment (fig 2). Most patients undergoing coronary angiography received cyclosporin treatment. No documented change in the incidence of coronary occlusive disease has occurred, however, with the various developments in immunosuppressive treatment here or elsewhere as yet.[4] This is shown by the similarity in slope of the decline in survival curves after the first year in each immunosuppressive treatment group (fig 2).

CORONARY ANGIOGRAPHY

We reviewed 447 coronary angiograms in 193 patients. Ninety nine patients had two or more coronary angiograms. Coronary occlusive disease was present in 3% (1/32) of patients undergoing coronary angiography by the first year, and 40% (19/47) at five years after operation. Figure 3 shows freedom from coronary occlusive disease as assessed on coronary angiography over seven years from transplantation. Coronary collateral vessels were seen to

Figure 3 Freedom from coronary occlusive disease as indicated by coronary angiography.



supply 12% (3/26) of the occluded coronary arteries in our study.

The severity of coronary stenosis produced by coronary occlusive disease was usually modest. For example, of the angiograms showing coronary occlusive disease in the left anterior descending coronary artery, 55% (61/110) showed lesions that decrease the diameter of affected vessels by <25% of the diameter of the adjacent arteries. Only 12% of the cine films (13/110) showed lesions of >50% stenosis in the left anterior descending coronary artery. Therefore, the degree of luminal obstruction was usually not severe. The disease, however, often affects different portions of the same artery as well as other vessels. This pattern of distribution of the disease makes accurate anatomical description difficult.

GRAFT FAILURE

Coronary occlusive disease caused failure of 26 grafts (20%) compared with 132 graft losses from all causes during this period. Most of these patients died later than one year after operation (table 1). Thirteen patients who had undergone coronary angiography died and the heart was available for full examination. Seven patients underwent eight cardiac retransplantation operations. The remaining five patients died and had necropsies, but the heart was not examined at this hospital.

The mean age of all patients at the time of graft failure was 39 (range 23–57) years. The median time from the identification of coronary occlusive disease angiographically to death in the group dying of coronary occlusive disease was 2·3 (range 0·1–5·6) years. Twelve of the 13 patients who died and had post mortem examinations had considerable cardiomegaly (weight ⩾400 g) with a mean overall weight of 507 (range 370–740) g.

Coronary angiograms were performed before graft failure in 18 of the patients who had pathology data available (table 2). Coronary angiography tended to underestimate the severity of the stenosis in coronary occlusive disease found at post mortem examination. It is, however, difficult to assess accurately the severity of stenosis in post mortem samples that have not been pressure perfused. This structural comparison is therefore limited in value.

MORTALITY

Thirteen patients died and underwent detailed post mortem examination. The mode of death was acute thrombosis on a significant lesion affecting a primary or secondary vessel in seven cases (table 2). In two of these patients there was evidence of old thrombus in different vessels to the ones affected by the acute thrombus. There was post mortem evidence of previous non-transmural myocardial infarction in two cases, and a recent infarction in one patient who died.

In four of the 13 patients undergoing post mortem examination there was histological evidence of coronary disease in small tertiary branches, as well as the large primary and secondary coronary vessels. Three patients died with diffuse involvement of small tertiary vessels alone. When disease in small coronary vessels was the only cause of death, coronary angiography did not detect coronary disease. It was performed in two of these cases before death, and appeared normal, and was not done in the remaining patient as death occurred before the first routine coronary angiogram was performed.

The time from the first sign of coronary disease to death progressively decreased as more primary coronary arteries were diseased, but the differences were not statistically significant (fig 4). Longer follow up in more patients is required to clarify this. Coronary occlusive disease was not detected on coronary angiography in 107 (55%) patients at any stage during during the study period. Eight of these patients have died: two of coronary occlusive disease, two of malignancy, two of sudden death, and two of other causes.

RETRANSPLANTATION

Seven patients were retransplanted for coronary occlusive disease. One patient required a further retransplant for recurrent coronary disease. The median time from transplantation to reoperation was 3·6 (range 0·3–8·8) years. These patients had progressive coronary disease that allowed elective reassessment for reoperation. Only three of these patients had coronary angiography performed on their second graft during the study period. Therefore there is insufficient data to assess angiographic recurrence of coronary disease in retransplanted patients.

Table 1 Causes of death in cardiac transplant patients between January 1979 and June 1990

	Time from transplantation		
Causes of death	*0–90 days*	*90 days–1 year*	*>1 year*
Rejection	23	9	1
Infection	21	8	3
Coronary occlusive disease	0	2	26
Sudden cardiac death	1	1	3
Donor heart failure	6	0	0
Stroke	4	1	0
High pulmonary resistance	4	0	0
Multifactorial	4	0	0
Lymphoma	1	0	2
Malignancy	0	1	5
Abdominal complications	2	0	0
Operative bleeding	1	0	0
Unknown	1	1	1
Total	68	23	41

Table 2 Post mortem data

Patient No	*Age (y)*	*TTF (y)*	*An*	*PM*	*Event*	*Wt of heart (g)*
1	29	3	NCA	2VD T	death	440
2	49	3 5	MINLVD	1VDT	death	400
3	50	1 7	NCA	1VD	death	600
4	52	5 9	3VD	LMain T 3VD MI(old)	death	510
5	23	8	MINLVD	2VD T	death	580
6	30	2 5	MINLVD	1VD Told	death	480
7	46	0 7	NCA	SVD	death	480
8	44	4	Cx	3VD	death	500
9	45	4	LVD-OM	1VD-T	death	480
10	52	4 5	NAD	SVD	death	740
11	26	2 8	3VD	3VD Told old and new MIs	death	390
12	36	1 9	3VD	1VD-T MI	death	610
13	28	1	NCA	1VD	death	670
14	25	3	NCA	SVD	RETX	440
15	35	8 8	2VD SVD	3VD	RETX	600
16	34	3 1	2VD	3VD	RETX	370
		1 2	2VD	3VD	RETX	370
17	21	4 4	NCA	2VD	RETX	480
18	36	5 2	3VD	3VD	RETX	545
19	26	4 1	3VD	3VD	RETX	510
20	57	0 3	NCA	SVD	RETX	470

TTF, time to graft failure, An, angiographic lesion or stenosis, PM, post mortem lesion or stenosis, NCA, no coronary arteriogram available, VD, vessel disease; T, fresh thrombus, MINLVD, minor disease in large epicardial coronary artery, SVD, disease in tertiary vessels on histology, LMain, left main coronary artery, T old, old thrombus; CX, left circumflex artery, LVD-OM, large vessel disease obtuse marginals, RETX, retransplanted; MI, myocardial infarction

Discussion

Coronary occlusive disease probably occurs as a result of responses to immunologically mediated vascular injury.[7] It may be related to the arteriopathy seen in other transplanted solid organ grafts.[8] Higher incidences of myocardial cellular rejection[9,10] and vascular (humoral) rejection[11] have been reported in patients developing coronary occlusive disease. Hyperlipidaemia, often exacerbated by steroid[12] and cyclosporin treatment,[13] is probably an important cofactor in the development of coronary occlusive disease. High total cholesterol, high LDL cholesterol,[13] and low HDL cholesterol concentrates,[14] and hypertryglyceridaemia[15] have been implicated in some studies. Cytomegalovirus infection has been suggested as a potential cause of the disorder.[16] The relation between virus infection and coronary occlusive disease has not been found at other centres.[14] There is no evidence, as yet, of cytomegalovirus causing direct coronary artery damage. Other factors have been reported as being associated with development of disease (table 3). The aetiology is unclear at present. No single factor appears to be so important that it stands out, because of the few patients studied. It is probable that coronary occlusive disease is a manifestation of chronic vascular rejection in combination with other cofactors.[22] Until the pathogenesis becomes clearer, appropriate preventive and therapeutic strategies are difficult to design.

Serial coronary angiography has been the main method of assessing coronary occlusive disease after cardiac transplantation. As a result of the previously described differences from conventional coronary artery disease, it underestimates the presence and severity of lesions. The reported prevalence of angiographic coronary occlusive disease after cardiac transplantation in other centres varies from between 2% and 18% at one year and 40% and 44% at five years.[4,23,24] The differences may partly represent variations in reporting criteria.[7]

It is clear from our study that angiographic evidence of coronary disease does not always accurately predict the prognosis in an individual patient. The low number of graft failures from coronary occlusive disease in transplant patients limits the comparisons with the large trials undertaken in conventional coronary artery disease.[25] The apparently increased risk of death in cardiac transplant patients with coronary disease may be due to the disturbed relation between coronary arterial structure, as defined by angiography, with coronary vascular and myocardial function. The concentric luminal narrowing, sequential stenoses, the diffuse nature of the disease, and the involvement of small vessels are responsible for the functional impairment. The few patients who have died from coronary occlusive disease precludes identification of potential associated risk factors for death.

Coronary disease with acute coronary thrombosis in primary and secondary vessels caused death in seven of 13 available cases as shown at post mortem examination. Most of these atheromatous plaques (six of seven) had considerable severity of stenosis. Again, reservations must occur regarding the accuracy of measurements of stenosis with these post mortem findings. This experience of plaque rupture as a cause of sudden death, however, is similar to that seen in coronary atherosclerotic

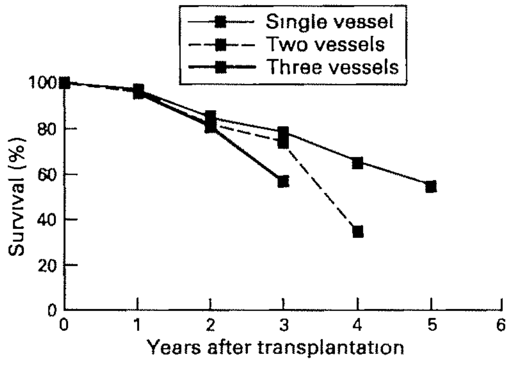


Figure 4 Survival from first angiographic evidence of coronary occlusive disease according to number of vessels affected.

Table 3 Risk factors associated with coronary occlusive disease

Factor	*Reference*
Hypertension	Becker *et al*[17]
Increased donor and recipient age	Sharples *et al*[18]
Ischaemic heart disease as indication for transplant	Sharples *et al*[14]
HLA mismatch and	Pennock *et al*[18]
Anti-HLA antibodies	Reemtsma *et al*[19]
Cytotoxic B cell antibodies	Hess *et al*[20]
Haemostatic factors (fibrinogen, VIIc, VIIIc)	Hunt *et al*[21]

disease in non-transplant patients. For example, in a series of 100 consecutive sudden coronary deaths, 44% had a >50% coronary arterial stenosis with a thrombosis.[26] It is also evident that most of the patients had considerable cardiomegaly. The cause of this is unclear, as the patients did not have untreated hypertension (two had treated hypertension). Presumably graft failure, at least in some patients, was a result of coronary occlusive disease in large and small vessels producing symptom free cardiac ischaemia in a denervated, hypertrophied heart. This resulted in myocardial infarction in some cases, and presumably, fatal arrythmias in all cases.

Coronary occlusive disease can produce several outcomes. Sudden plaque rupture is unpredictable and leads to infarction or death in both conventional and transplant coronary disease.[5] In progressive coronary occlusive disease leading to left ventricular dysfunction, full assessment for further treatment can be made. At present, cardiac retransplantation is the only established treatment. Unfortunately, survival outcome is poorer than for first time transplant patients,[1] and the recurrence rates of coronary occlusive disease are higher.[27] Justifying such treatment in the face of acute donor shortage is dificult.[28] Percutaneous transluminal coronary angioplasty can be used to dilate discrete lesions in the proximal coronary arteries in cardiac transplant patients. The short-term results are comparable with the effectiveness in conventional atherosclerosis.[29] Its long-term impact on cardiac function and prognosis is unclear. The use of coronary artery bypass grafting has been limited, as distal coronary vessels suitable for surgery are rare.[30]

The lack of suitable treatment for coronary occlusive disease calls into question the clinical value of routine coronary angiography in the follow up of symptom free cardiac transplant patients after operation. This contrasts with its research role, where it is clear that although more patients are required, risk factor analysis may eventually provide insights into associated cofactors in development of disease. The presence of severe lesions in larger coronary arteries is likely to be associated with a poor prognosis as suggested by our study. The mortality data, however, suggests that moderate epicardial coronary disease and disease in smaller vessels are also important in the increased mortality in long-term heart transplant patients. Ventricular hypertrophy may also be an important risk factor.

Non-invasive methods of detection of coronary occlusive disease have been disappointing.[31] We should therefore attempt to use newer methods of measuring impairment of myocardial perfusion and function produced by coronary occlusive disease.[32] With this information, improved preventive and therapeutic strategies for long-term cardiac transplant patients with coronary occlusive disease could be made.

In conclusion coronary occlusive disease is the main cause of late mortality and morbidity in cardiac transplant patients. Coronary disease affecting primary and secondary coronary arteries is the main factor in late mortality after cardiac transplantation, although disease in smaller distal vessels and ventricular hypertrophy are also implicated. Improved methods of measuring impairment of myocardial perfusion and function produced by coronary occlusive disease should be developed.

1 Kriett JM, Kaye MP. The registry of the international heart transplant registry seventh official report. *J Heart Lung Transplant* 1990;**9**:323–36.

2 Billingham ME. Cardiac transplant atherosclerosis. *Transplant Proc* 1987;**4**(suppl 5):19–25.

3 Johnson DE, Gao SZ, Schroeder JS, De Campli WM, Billingham ME. The spectrum of coronary artery pathologic findings in human cardiac allografts. *J Heart Transplant* 1989;**8**(5):349–59.

4 Gao SZ, Alderman EL, Schroeder JS, Silverman JF, Hunt SA. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. *J Am Coll Cardiol* 1988;**12**:334–40.

5 Gao SZ, JS Schroeder, SA Hunt, ME Billingham, HA Valantine, EB Stinson. Acute myocardial infarction in cardiac transplant patients. *Am J Cardiol* 1989;**64**:1093–7.

6 Pomerance A, Davies MJ. In: *The pathology of the heart*. Oxford: Blackwell Scientific Publications, 1975:45.

7 Schroeder JS, Hunt SA. Chest pain in heart transplant patients. *N Eng J Med* 1991;**324**:1805–6.

8 Kountz SL, Williams MA, Williams PL, Kapros C, Dempster WJ. Mechanism of rejection of homotransplanted kidneys. *Nature* 1963;**199**:257–99.

9 Zusman DR, Stinson EB, Oyer PE, Baldwin JC, Jamieson SW, McGregor CG, *et al*. Determinants of accelerated graft atherosclerosis (AGAS) in conventional and cyclosporine treated heart transplant recipients [abstract]. *J Heart Transplant* 1985;**4**:587.

10 Narrod J, Kormos R, Armitage J, Hardesty R, Ladowski J, Griffith B. Acute rejection and coronary artery disease in long-term survivors of heart transplantation. *J Heart Transplant* 1989;**8**:418–20.

11 Hammond EH, Yowell RL, Nunoda S, *et al*. Vascular (humoral) rejection in heart transplantation: pathologic observations and clinical implications. *J Heart Transplant* 1989;**8**:430–43.

12 Ratkovec RM, Wray RB, Renlund DG, O'Connell JB, Bristow MR, Gay WA, *et al*. Influence of corticosteroid-free maintenance immunosuppression on allograft coronary artery disease after cardiac transplantation. *J Thorac Cardiovasc Surg* 1990;**100**:6–12.

13 Stamler JS, Vaughan DE, Rudd MA, *et al*. Frequency of hypercholesterolaemia after cardiac transplantation. *Am J Cardiol* 1988;**62**:1268–72.

14 Sharples LD, Caine N, Mullins P, Scott JP, Solis E, English TAH, *et al*. Risk factor analysis for the major hazards following heart transplantation—rejection, infection and coronary occlusive disease. *Transplantation* 1991;**52**:244–52.

15 Gao SZ, Schroeder JS, Alderman EL, Hunt SA, Valantine HA, Wiedrehold V, Stinson EB. Prevalence of accelerated coronary artery disease in heart transplant survivors. Comparison of cyclosporine and azathioprine regimens. *Circulation* 1989;**80**:100–5.

16 Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *JAMA* 1989;**261**:3561–6.

17 Becker DM, Markakis BS, Sension M, Vitali S, Baughman K, Pearson TA. Hyperlipidaemia and hypertension following heart transplantation: potential causes of coronary atherosclerosis [abstract]. *J Am Coll Cardiol* 1986;7:9.

18 Pennock JL, Oyer PE, Reitz BA, Jamieson SW, Bieber CP, Wallwork J, *et al*. Cardiac transplantation in perspective for the future: survival, complications, rehabilitation and cost. *J Thorac Cardioavasc Surg* 1982;**83**:168–77.

19 Reemtsma K. Vascular immunoobliterative disease: a common cause of graft failure. *Transplant Proc* 1989;**21**:3706.

20 Hess ML, Hastillo A, Mohanakumar T, Cowley MJ, Vetrovac G, Szentpery S, *et al*. Accelerated atherosclerosis in cardiac transplantation: role of cytotoxic B-cell antibodies and hyperlipidaemia. *Circulation* 1983;**68**:94–101.

21 Hunt B, Segal H, Yacoub M. Haemostatic changes after

heart transplantation and their relationship to accelerated coronary atherosclerosis. *Transplant Proc* 1991;23:1233–5.

22 Stovin PG, Sharples L, Hutter JA, Wallwork J, English TAH. Some prognostic factors for the development of transplant-related coronary artery disease in human cardiac allografts. *J Heart Lung Transplant* 1991;10:38–44.

23 O'Neill BJ, Pflugfelder PW, Singh NR, Menkis AH, M'cKenzie FN, Kostuk WJ. Frequency of angiographic detection and quantitative assessment of coronary arterial disease one and three years after cardiac transplantation. *Am J Cardiol* 1989;63:1221–6

24 Uretsky BF, Murali S, Reddy PS, Rabin B, Lee A, Griffith BP, *et al*. Development of coronary artery disease in cardiac transplant patients receiving immunosuppressive therapy with cyclosporine and prednisone. *Circulation* 1987,76:827–34.

25 Killip T, Passami E, Davis K, *et al*. Coronary artery surgery study: a randomized trial of coronary bypass surgery. Eight year follow-up and survival in patients with reduced ejection fraction. *Circulation* 1985;72(suppl V):102–12.

26 Davies MJ, Thomas A. Thrombosis and acute coronary lesions in sudden cardiac ischaemic death. *N Engl J Med* 1984,310:1137.

27 Gao SZ, Schroeder JS, Hunt SA, Stinson EB. Retransplantation for severe accelerated coronary artery disease in heart transplant recipients. *Am J Cardiol* 1988;62:876–81.

28 Mullins PA, Scott JP, Dunning JJ, Aravot DJ, Large SR, Wallwork J, Schofield PM Cardiac transplant waiting lists, donor shortage and retransplantation and implications for using donor hearts. *Am J Cardiol* 1991;68:408–9.

29 Copeland JG, Butman SM, Sethi G. Successful coronary artery bypass grafting for high-risk left main coronary artery stenosis after cardiac transplantation. *Ann Thorac Surg* 1991;49:106–10.

30 Mullins PA, Shapiro LM, Aravot DJ, Scott JP, Large SR, Wallwork J, Schofield PM. Experience of PTCA in orthotopic cardiac transplant recipients. *Eur Heart J* 1991,12.1205–8

31 Smart FW, Ballantyne CM, Cocanougher B, Farmer JA, Sekela ME, Noon GP, Young JB. Insensitivity of non-invasive tests to detect coronary artery vasculopathy after heart transplant *Am J Cardiol* 1991,67:243–7.

32 Mullins PA, Scott JP, Aravot DJ, Large SR, Wallwork J, Schofield PM. Small vessel coronary occlusive disease after cardiac transplantation [abstract]. *J Am Coll Cardiol* 1991;17.308.

Br Heart J 1992;**68**:266–71

Impairment of coronary flow reserve in orthotopic cardiac transplant recipients with minor coronary occlusive disease

P A Mullins, A Chauhan, L Sharples, N R Cary, S R Large, J Wallwork, P M Schofield

Abstract

Objective—Coronary occlusive disease is the major long-term complication after cardiac transplantation. The relation between minor angiographic abnormalities and myocardial perfusion has not been previously assessed in a large number of cardiac transplant patients.

Design—Prospective study. Coronary flow reserve was measured with an intracoronary Doppler flow probe in the proximal left anterior descending coronary artery in each patient. A dose of intracoronary papaverine producing maximal vasodilation was then administered.

Setting—A regional cardiothoracic centre and a supraregional transplant unit.

Patients—Seven patients with chest pain but normal coronary anatomy (controls), and 61 cardiac transplant patients between three months and 10 years after operation (median 4·5 years). Twenty one cardiac transplant patients had angiographic evidence of minor coronary occlusive disease (mean (SD) percentage stenosis diameter 23% (6%)) in a primary or secondary coronary vessel (group 1), with 12 of these in the left anterior descending coronary artery (stenosis diameter (mean (SD) 24% (8%)). The remaining 40 transplant patients had normal coronary angiograms (group 2).

Main outcome measure—Coronary flow reserve was defined as the ratio of the peak flow velocity after papaverine to the resting flow velocity.

Results—Group 1 patients had a noticeably impaired coronary flow reserve (2·6 (1·1)) compared with control patients (3·9 (0·4), $p = 0.05$) and, after adjusting for year after operation, compared with group 2 patients (3·8 (1·0), $p < 0.001$). No other variables were associated with a reduction in coronary flow reserve. Mean resting flow velocity was similar in all three groups (controls, 7·4 (4·6) cm/s; group 1, 7·5 (5·9) cm/s; and group 2, 7·3 (3·9) cm/s). Mean peak flow velocity response to papaverine was reduced in group 1 patients (18·1 (13·5) cm/s) relative to group 2 patients (27·5 (15·4) cm/s, $p = 0.05$) but not controls (28·4 (15·1) cm/s, $p = 0.1$).

Conclusions—Coronary flow reserve and the peak flow response to the coronary vascular smooth muscle relaxant papaverine are impaired in cardiac transplant patients with minor coronary occlusive disease. This disturbance of cardiac microvascular function may contribute to the late morbidity and mortality seen in cardiac transplant patients with coronary occlusive disease.

(*Br Heart J* 1992;**68**:266–71)

Transplant Unit,
Papworth Hospital,
Papworth Everard,
Huntingdon,
Cambridge
P A Mullins
A Chauhan
L Sharples
N R Cary
S R Large
J Wallwork
P M Schofield

Correspondence to
Dr P A Mullins, Transplant
Unit, Papworth Hospital,
Papworth Everard,
Huntingdon, Cambridge
CB3 8RE.

Accepted for publication
28 November 1991

Coronary occlusive disease is the main cause of morbidity and mortality more than one year after orthotopic cardiac transplantion.[1] Clinical monitoring of the disease has been dependent on serial coronary angiography. This method is insensitive at detecting coronary occlusive disease in heart transplant patients[2 3] and underestimates it's presence compared with postmortem data.[4] This is due to the concentric and tubular nature of the disease and it's involvement with the whole length of the coronary arteries, (fig 1).[1] It also affects small and medium sized coronary vessels. It is not possible to assess all of these vessels angiographically. Attempts to classify coronary occlusive disease in all vessels including distal arteries have been made, but the relation between coronary anatomy as seen on angiography and prognosis is still not clear.[3]

Coronary angiographic assessment of both conventional and transplant related coronary

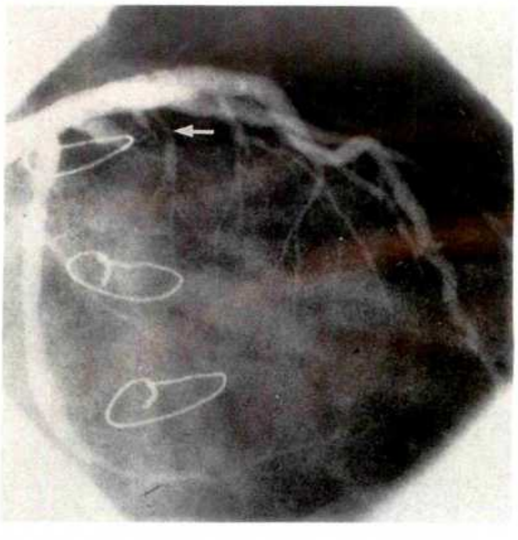


Figure 1 Right anterior oblique view showing diffuse irregularity of left anterior descending and left circumflex coronary arteries. Arrow shows disease in septal perforating branch.

occlusive disease has other limitations. For example, the assumption that narrowings of intermediate severity are not physiologically significant is questioned.[5] Coronary flow reserve measurements are increasingly used as potential methods of estimating the physiological impact of coronary pathology,[6] including coronary disease which may affect small vessels.[7] Coronary flow reserve is defined as the ratio of the maximum to the resting coronary flow at a given perfusion pressure, when coronary vessels are maximally vasodilated. In the normal coronary circulation, coronary flow reserve is reduced by lesions producing about 35%–59% stenosis or more in primary coronary arteries.[5 8 9] To maintain myocardial blood flow, coronary resistance vessels vasodilate to compensate for the resistance offered by proximal stenoses.[9] The maximal flow at a given coronary perfusion pressure depends predominantly upon the total cross sectional area of the resistance vessels. A reduction in the number or calibre or impaired function of these coronary resistance vessels could have considerable impact on coronary flow reserve. This may limit their ability to respond to reductions in myocardial flow produced by proximal coronary lesions.[10]

Until recently, inaccuracy has limited methods of assessing effective coronary blood flow. The use of small diameter (3 French) intracoronary Doppler flow catheters allows subselective estimations of coronary blood velocity in individual coronary vessels.[11 12] This is a simple reproducible method of evaluating coronary flow reserve when used in conjunction with vasodilators, particularly papaverine.[13] This technique has been more extensively evaluated than any other currently used.[8] We investigated the effects of coronary occlusive disease on coronary flow reserved in cardiac transplant recipients with this technique.

Patients and methods

PATIENTS

Studies were performed in seven non-cardiac transplant patients (controls) with chest pain but without significant coronary disease who were undergoing coronary angiography as part of a separate study. Sixty one patients (56 men) were investigated after cardiac transplantation.

IMMUNOSUPPRESSIVE REGIMEN AND DRUG TREATMENT

All cardiac transplant patients were receiving cyclosporin and azathioprine immunosuppression with or without steroid treatment. None of the patients were taking β antagonist treatment. All vasoactive medication (for example calcium antagonists) was stopped 24 hours before operation. None of the patients received premedication.

BIOPSY PROTOCOL

All cardiac transplant patients underwent right ventricular endomyocardial biopsy on the day of coronary angiography. These samples were examined by conventional light microscopy and graded according to standard histological criteria for the presence of acute rejection.[14]

BLOOD ANALYSIS

Blood was analysed routinely for full blood count, urea and electrolytes, liver function tests, fasting lipids (total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and serum triglycerides), and trough whole blood cyclosporin concentration on the day of study.

ECHOCARDIOGRAPHY

Routine echocardiographic assessment was performed with cross sectional and M mode evaluation of left ventricular posterior wall and septal thickness. To reduce any effect on coronary flow measurements produced by left ventricular hypertrophy patients with a diastolic septal or posterior wall thickness of more than 11 mm were not included in the study.

CATHETERISATION PROTOCOL

The patients fasted before cardiac catheterisation. Coronary angiography was performed by the Judkins technique through the right femoral artery in all patients. Coronary injections were performed manually with up to 8 ml of intracoronary radio-opaque contrast (Niopam) and cine film recordings were made in multiple projections. After routine angiography the proximal left anterior descending coronary artery was centred for optimal viewing. To eliminate vasoactive effects from the contrast medium at least 10 minutes elapsed before the study continued.

Heparin (10 000 units) was given intravenously. A size 8F angioplasty guiding catheter was placed into the left coronary ostium and a 0·014 inch guide wire into the distal part of the left anterior descending coronary artery. With a monorail technique, a size 3F 20 MHz intracoronary Doppler flow probe (Schneider, UK) was placed over the guide wire into the proximal segment of the left anterior descending coronary artery. The Doppler flow probe and the range gate of the velocimeter were adjusted to get good quality phasic and mean coronary blood flow velocity signals. These signals were recorded with the surface electrocardiogram on a Mingograf recorder (Siemens-Elema, Sweden).

Baseline mean resting and phasic coronary blood flow velocity were taken in each patient. After an initial intracoronary 2 mg test dose of papaverine hydrochloride through the guiding catheter, further injections of up to 14 mg of papaverine (2 mg per ml in 0·9% saline) were given in 2 mg increments until maximum flow was achieved. The hyperaemic response was recorded in the form of maximum mean and phasic blood flow velocity (cm/s) (fig 2). Velocity profiles were allowed to return to baseline between doses of papaverine.

CORONARY ANGIOGRAPHY

Each coronary angiogram was assessed by two independent observers blinded to the clinical history. Coronary occlusive disease was defined as any evidence of disease on the angiogram in

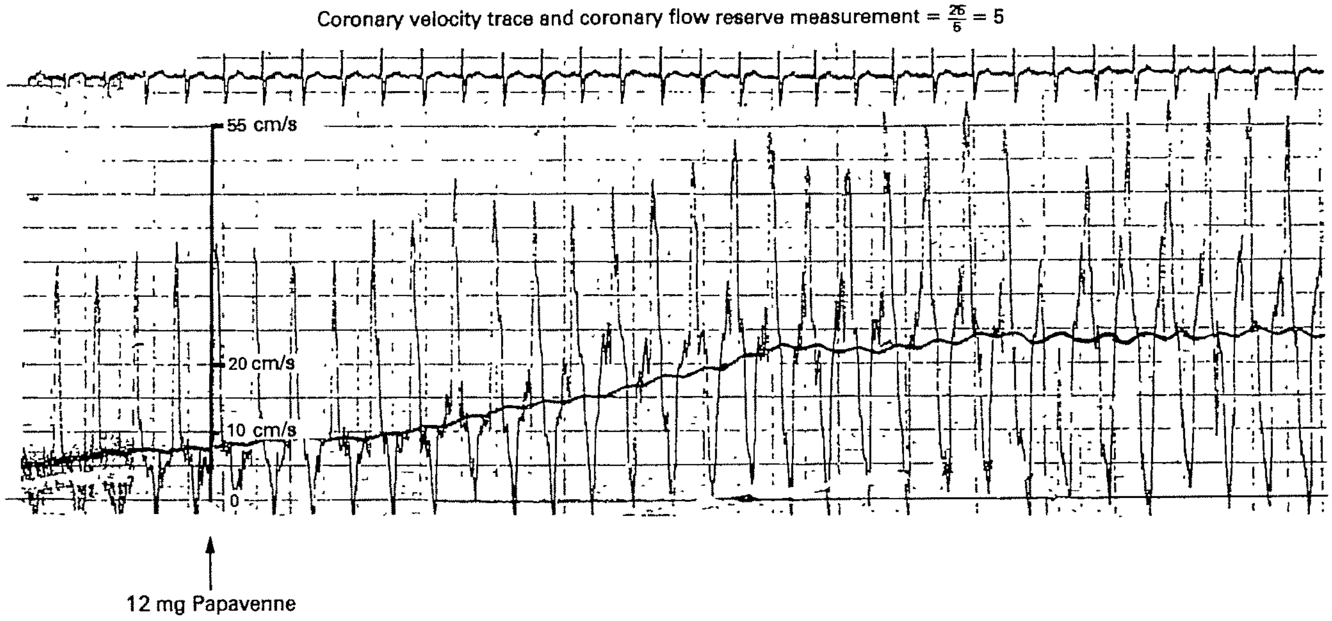


Figure 2 Increased coronary blood flow velocity after an intracoronary injection of 12 mg of papaverine hydrochloride.

primary or secondary coronary arteries. The primary coronary arteries were defined as the left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery. Their main branches (the diagonal, obtuse marginal, and posterolateral or posterior descending branch of the right coronary artery) were classified as secondary coronary arteries.

Coronary disease was graded according to the stenosis diameter of the most severe lesion in primary or secondary coronary vessels compared with an adjacent healthy artery. The coronary lumen was defined as the effective perfusion channel and was measured in diastolic frames. Quantitative measurements of arterial diameter in coronary vessels were taken with digital electronic calipers (Sandhill Scientific Inc). This method was used in studies examining both progression of coronary occlusive disease[2] and coronary flow reserve.[15] Two views were taken and projected by a Tagarno system on to a sheet of paper. The arterial diameter was measured in the left anterior descending coronary artery from tracings of the projected image in diastole, at a distance of 2–3 mm from the tip of the Doppler flow probe. The diameters were calculated as the mean of the meaurements of these two views. The most severe lesion in the coronary arterial tree was measured by the same method. Coronary angiography was performed at rest and at peak hyperaemia, and changes in coronary diameter were measured. Left ventricular angiography was performed at the end of the study. Patients with evidence of left ventricular wall motion abnormalities in the region supplied by the left anterior descending coronary artery were not included.

CORONARY FLOW RESERVE AND CORONARY VASCULAR RESISTANCE INDEX

Figure 2 shows that coronary flow reserve (CFR) was defined as the ratio of the peak flow velocity (PFV) to the resting blood flow velocity (RFV). To offset any changes in blood pressure during the study, a coronary vascular resistance index (CVRI) was calculated:

$$\text{CVRI} = \frac{\text{mean BP at peak flow/PFV}}{\text{mean BP at rest/RFV}}$$

where BP = aortic blood pressure.

STATISTICAL ANALYSIS

Results are expressed as means (SD) for continuous measurements, and frequencies for categorical variables. The three groups were compared in pairs by Bonferroni's method to compensate for multiple non-independent testing. To avoid bias, logistic regression analysis was used to adjust coronary flow reserve measurements for the year after operation in the transplanted groups, and comparisons were made by the likelihood ratio test. Statistical significance was assumed for $p \leqslant 0{\cdot}05$.

ETHICAL COMMITTEE APPROVAL

This study was approved by the Huntingdon District Health Authority Ethical Committee.

Results

PATIENT DETAILS

The seven control patients underwent repeat coronary angiography and coronary flow reserve investigations as part of a separate study. Tables 1 and 2 show relevant patient information, haemodynamic measurements, and other variables for all groups.

The median time from operation for all cardiac transplant patients was 4·5 years (range three months to 10 years). Of the transplanted patients, 31 originally underwent transplantation for ischaemic heart disease, and the remaining 30 patients for dilated cardiomyopathy. Group 1 cardiac transplant patients were significantly further from operation compared with group 2 patients (Mann-Whitney $z = 2{\cdot}7$, $p < 0{\cdot}007$). Variables that could potentially be related to the development of

Table 1 Patient variables (mean (SD))

	Heart rate	*MAP (mm Hg)*	*LVEDP (mm Hg)*	*Age (y)*	*Sex*	*Hct (%)*
Control patients (n = 7)	84 (11)	96 (6)	8 (5)	52 (12)	M = 4, W = 3	43 (2·0)
Group 1 (n = 21)	87 (11)	96 (3)	9 (1)	45 (12)	M = 20, W = 1	40 (0·3)
Group 2 (n = 40)	83 (19)	94 (3)	8 (2)	49 (9)	M = 36, W = 4	38 (0·4)

Controls, non-transplanted patients; group 1, cardiac transplant patients with minor coronary occlusive disease; group 2, cardiac transplant patients without coronary occlusive disease; MAP, mean arterial pressure; LVEDP, left ventricular end diastolic pressure; M, men; W, women, Hct, haematocrit.

Table 2 Demographic data (mean (SD))

	Controls	*Group 1 (n = 21)*	*Group 2 (n = 40)*
Original diagnosis	—	IHD 9 DCM 12	IHD 22 DCM 18
Median time after operation	—	5 (range 0·3–10 y)	4 (range 0·3–8 y)
Ischaemic time	—	152 min (43)	165 min (41)
Cy A concentration	—	308 (253)	326 (218)
Cholesterol	6·4 (0·9)	6·2 (1·4)	5·7 (1·9)
High density lipoprotein cholesterol	1·0 (0·2)	1·0 (0·3)	1·1 (0·4)
Low density lipoprotein cholesterol	4·7 (0·8)	5·1 (1·4)	4·7 (1·4)
Triglyceride	1·8 (0·6)	2·2 (1·3)	1·9 (0·6)

Footnotes as for Table 1 and; COD, coronary occlusive disease; Cy A, cyclosporin; DCM, dilated cardiomyopathy; IHD, ischaemic heart disease.

Table 3 Values calculated from coronary velocity trace (mean (SD))

	CFR	*CVRI*	*RFV*	*PFV*
Controls (n = 7)	3·9 (0·4)	0·27 (0·13)	7·4 (4·6)	28·4 (15·4)
Group 1 (n = 21)	2·6 (1·1)	0·4 (0·21)	7·5 (5·9)	18·1 (13·5)
Group 2 (n = 40)	3·8 (1·0)	0·26 (0·12)	7·3 (3·9)	27·5 (15·4)

CFR, coronary flow reserve; CVRI, coronary vascular resistance index; RFV, resting flow velocity (cm/s); PFV, peak flow velocity (cm/s).

coronary occlusive disease were similar in the three groups (table 2). The mean age of the donor hearts was 27 (11·7) years. The mean cold ischaemic time was 159 min (range 77–260 min). Sixteen (26%) of patients had received organs from female donors.

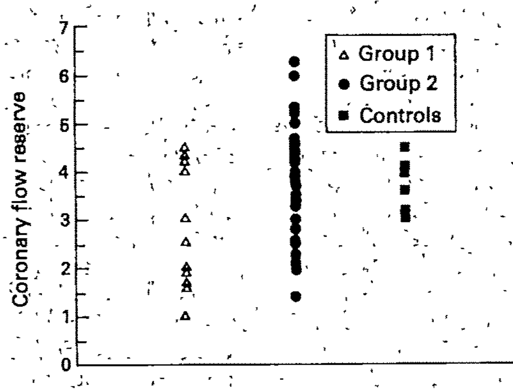


Figure 3 Coronary flow reserve of groups after cardiac transplantation and relation to coronary occlusive disease.

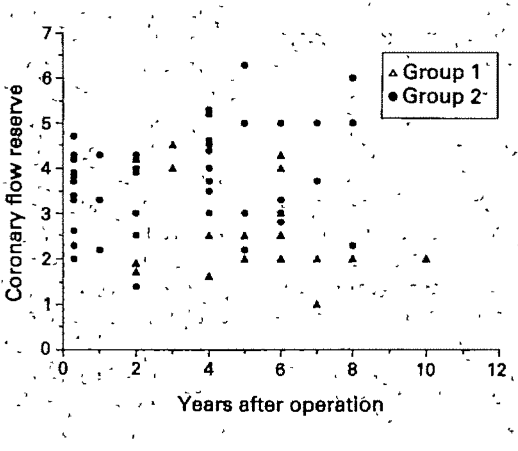


Figure 4 Coronary flow reserve after cardiac transplantation and time since operation.

CORONARY ANGIOGRAPHY

Of the seven controls, six patients did not have any evidence of coronary disease on angiography. The remaining patient had a minor lesion (23% stenosis) in the left circumflex coronary artery. Forty cardiac transplant patients had normal coronary angiograms, but 21 transplant patients had minor lesions in epicardial vessels; the mean percentage diameter of the most severe lesion in the coronary tree was 23% (6%) including 12 lesions in the left anterior descending coronary artery itself (mean percentage diameter 24% (8%)). Nine of these patients had minor coronary disease in one primary or secondary vessel, four patients had disease in two vessels and the remainder had disease in three or more coronary arteries.

CORONARY FLOW RESERVE MEASUREMENTS

Figure 3 shows coronary flow reserve measurements taken in all patients. After adjustment for year from operation (fig 4), group 1 patients had a significantly impaired coronary flow reserve and a higher coronary vascular resistance index compared with group 2 patients (likelihood ratio statistic = 18·5, $p < 0.001$, (table 3). Coronary flow reserve was also reduced compared with the control group ($p = 0.05$). The mean resting coronary blood flow was similar in the three groups. Mean peak flow velocity was impaired in patients with minor coronary occlusive disease compared with group 2 patients ($p = 0.05$), but not controls although there was a trend towards this ($p = 0.1$). There was mean overall dilatation by 17% of the left anterior descending coronary artery in all groups in response to papaverine (table 4). Arterial diameter measurements were acceptably reproduced with minimal interobserver ($r = 0.91$) and intraobserver variation ($r = 0.95$).

ENDOMYOCARDIAL BIOPSY

A mean of two rejection episodes had occurred in each cardiac transplant patient at some time after transplantation (range 0–8 episodes). Acute rejection was present in only three patients during the study. The coronary flow reserve of these patients (mean CFR 4·0 (1·1))

Table 4 Details of vasodilatation (mean (SD))

	Resting LAD diameter (mm)	*Diameter after papaverine*
Controls (n = 7)	4·4 (0·5)	4·9 (0·9)
Group 1 (n = 21)	3·6 (0·9)	4·3 (1·1)
Group 2 (n = 40)	4·0 (0·8)	4·9 (0·3)

LAD, left anterior descending coronary artery

P25748

was similar to patients without coronary occlusive disease (mean CFR 3·8 (1·0)).

COMPLICATIONS

One transplant patient had a short episode (less than 5 s) of non-sustained, symptom free, ventricular tachycardia. This has previously been described in response to intracoronary papaverine.[16 17] Another transplant patient had a brief respiratory arrest due to a reaction with the radiopaque contrast medium. There were no complications in the control group of patients.

Discussion

Our study shows that impairment of coronary flow reserve and maximum hyperaemic coronary blood flow is present in cardiac transplant patients who show minor large vessel coronary occlusive disease on an angiogram. The degree of stenosis in the conduit (left anterior descending) coronary artery was minor and affected this vessel in only 12 of 21 (57%) of patients. Also there were no differences between the groups in the degree of vasodilation produced by papaverine in the proximal left anterior descending coronary artery. This suggests vasodilatory dysfunction in the coronary resistance vessels in these patients.

The reduction in coronary flow reserve and maximum hyperaemic coronary flow could be explained by a reduction in the number of resistance vessels as coronary occlusive disease progresses.[18] Work on animals suggests that the precapillary resistance vessels of over 100 μm are responsible for roughly half the total coronary vascular resistance.[18] Deficits in coronary flow can be mediated by the direct effects of coronary occlusive disease on small vessels with diameters above this size. Occlusion of small tertiary (branches of primary and secondary coronary vessels) coronary branches is commonly seen post mortem,[19] but would have to be extremely widespread to have such a large effect on its own. Vasodilatory function of the vascular smooth muscle of resistance vessels may also be disturbed during the development of coronary occlusive disease. It is possible that both these factors may operate. Clinically, diffuse disease of the small vessels in cardiac transplant recipients is important. It can be the sole cause of progressive cardiac dysfunction and death in some patients, and may contribute to considerable disturbance of perfusion by modest primary coronary artery stenoses.[19]

Other alternative explanations for impairment of coronary flow reserve and peak coronary flow in the group with coronary occlusive disease need to be excluded. There were no obvious significant differences in heart rate, myocardial contractility, ventricular dilatation, raised left ventricular end diastolic pressure, or in haematocrit concentrations between the three groups.[19] Although the resting heart rate in patients with a denervated cardiac transplant is often higher than in normal patients, the lack of premedication in the control patients probably accounts for the lack of difference in heart rates at the time of the study. It is known that left ventricular hypertrophy, ventricular wall motion abnormalities and collateral vessels can produce abnormal flow reserve measurements.[8] None of the patients had these features. It is noteworthy that collateral vessels in heart transplant patients are unusual.[5] This may also be a reflection of dysfunction in smaller coronary vessels.

The mechanisms leading to the development of coronary occlusive disease and disturbance of coronary vascular function are not clear. Coronary occlusive disease probably occurs as a result of responses to immunologically mediated vascular injury.[20] It may be related to the arteriopathy seen in other solid organ transplanted grafts.[21] Higher incidences of myocardial cellular rejection[21–23] and vascular (humoral) rejection[24] have been reported in patients developing coronary occlusive disease. Hyperlipidaemia, often exacerbated by steroid[25] and cyclosporin treatment,[26] may be a cofactor in the development of coronary occlusive disease in some cardiac transplant patients. Cytomegalovirus infection has been suggested as a potential cause of coronary occlusive disease.[27] We did not find any association between myocardial rejection, lipids, cytomegalovirus or evidence of infection, and coronary flow measurements in patients with transplants. Group 1 patients, however, had minor coronary artery disease affecting the primary and secondary coronary arteries. It is possible that these factors are not important in producing vasomotor dysfunction in the coronary microcirculation, but contribute to the development of coronary occlusive disease in larger coronary arteries.

It was also evident that acute cellular rejection did not have an important effect on coronary flow reserve in the few patients with acute rejection at the time of investigation. One study has suggested that there is severe impairment of coronary flow reserve during acute myocardial cellular rejection,[28] but less reliable methods of measurement were used. This finding was not confirmed by other workers with similar techniques to ours.[29] We also did not find any evidence of vascular rejection on endomyocardial biopsy with conventional light microscopy. It has been noted that vascular rejection as seen by immunofluorescence techniques occurs up to about four weeks after transplantation.[24] More sensitive techniques need to be developed to be sure that persistent immunologically mediated vascular damage in heart transplant patients is not occurring. This may not only be directed at major histocompatibility complex related vascular antigens.[30]

Cyclosporin could potentially produce differences in coronary flow reserve due to vasoactive effects.[31 32] It has been suggested specifically that coronary flow reserve may be affected by cyclosporin concentrations in heart transplant patients.[29] We found no effect produced by trough whole blood cyclosporin concentrations in our patients.

This study confirms previous findings that cardiac transplant patients who do not have coronary occlusive disease have a similar coronary flow reserve and coronary resistance to non-transplanted controls.[33 34] It has been suggested in one study that patients with mild to moderate degrees of coronary occlusive disease do not have impaired vasodilator reserve.[34] Only five cardiac transplant patients with coronary disease were actually studied, however, and some of these may have been taking β antagonist agents that would affect coronary flow measurements. Also, our cardiac patients with transplant coronary disease were studied at a longer interval after operation (mean 5, range 0·3–10 years) than in the previous study (mean 3·3, range 1–4·75 years). Therefore coronary microcirculatory dysfunction may have been more advanced in our patients.

Functional assessment of the coronary vasculature in patients with coronary occlusive disease is preferable to anatomical visualisation of the lumen of the proximal coronary arterial tree. Intracoronary flow techniques are fairly safe and reliable and can give this additional information. Non-invasive assessment of coronary perfusion and flow reserve are important alternative approaches that should be developed further.[35] Isotope perfusion studies show impaired myocardial perfusion in the absence of allograft rejection and significant epicardial disease.[36] This may parallel impairment of coronary flow reserve and explain these perfusion abnormalities.

The clinical importance of the measured reductions in coronary flow reserve and peak hyperaemic response in individual cardiac transplant patients is uncertain at this early stage. Progressive myocardial dysfunction and increased mortality could occur in the patients with lower coronary flow reserve. Some patients with apparently normal coronary angiograms have impaired coronary flow reserve. These patients may have distal coronary occlusive disease that is not seen on angiography. Longitudinal studies are now underway to evaluate the relevance of these findings.

CONCLUSION

Coronary flow reserve and hyperaemic response to the non-endothelial dependent vasodilator, papaverine, is significantly impaired in heart transplant recipients when minor coronary occlusive disease is identified by coronary angiography. Dysfunction of the coronary microcirculation may contribute to the considerable late morbidity and mortality produced by the disease. This may prove an important method of evaluating coronary occlusive disease in patients after cardiac transplantation.

We thank Dr G I Verney and staff of the *x* ray and cardiac technical departments at Papworth Hospital for their support during this study

1 Kriett JM, Kayne MP. The registry of the international heart transplant registry seventh official report—1990 *J Heart Lung Transplant* 1990,9.323–36
2 O'Neill BJ, Pflugfelder PW, Singh NR, Menkis AH, McKenzie FN, Kostuk WJ Frequency of angiographic detection and quantitative assessment of coronary arterial disease one and three years after cardiac transplantation. *Am J Cardiol* 1989,63·1221–6.
3 Gao SZ, Alderman EL, Schroeder JS, Silverman JF, Hunt SA Accelerated coronary vascular disease in the heart transplant patient coronary angiographic findings *J Am Coll Cardiol* 1988,12 334–40
4 Uys CJ, Rose AG Pathologic findings in long-term cardiac transplants *Arch Pathol Lab Med* 1984;108 112–6
5 Marcus ML, Skorton DJ, Johnson MR, Collins SM, Harrison DG, Kerber RE. Visual estimates of percent diameter coronary stenosis: "a battered gold standard" *J Am Coll Cardiol* 1988;11 882–5
6 Buss PD. The coronary circulation In Nichols WM, O'Rourke ME eds *McDonald's Blood Flow in Arteries* London Edward Arnold 1990, 360–80
7 Opherk D, Zebe H, Weihe E, *et al* Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary angiograms *Circulation* 1981,63:817–25
8 Hartley CJ. Review of intracoronary Doppler catheters *Int J Card Imaging* 1989,4 159–68.
9 Klocke FJ. Measurements of coronary flow reserve defining pathophysiology versus making decisions about patient care. *Circulation* 1987,76 1183–9
10 Gould KL, Lipscomb K, Calvert C Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. *Circulation* 1975,51:1085–94
11 Hoffman JF Maximal coronary flow and the concept of coronary vascular reserve *Circulation* 1984,70 153–9
12 Wilson RF, Laughlin DE, Ackell PH, Chilian WM, Holida MD, Hartley CJ, *et al* Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. *Circulation* 1985,72 82–92
13 Hoffman JF A critical view of coronary reserve *Circulation* 1987,75(suppl 1) 1–6
14 Billingham ME Diagnosis of cardiac rejection by endomyocardial biopsy *J Heart Transplant* 1981;1 25–30.
15 Kern MJ, Deligonul U, Vandormael M, *et al* Impaired coronary vasodilator reserve in the immediate post-coronary angioplasty period analysis of coronary artery flow velocity indexes and regional cardiac venous efflux. *J Am Coll Cardiol* 1989,1 869–72
16 Wilson RF, White CF Intracoronary papaverine an ideal vasodilator for studies of the coronary circulation in conscious humans *Circulation* 1986;73 444–51
17 Talman CL, Winniford MD, Rossen JD, Simmonetti I, Kienzle MG, Marcus ML Polymorphous ventricular tachycardia a side effect of intracoronary papaverine *J Am Coll Cardiol* 1990,15 275–8
18 Marcus ML, Chilian WM, Kanatsuka H, Dellsperger KC, Eastham CL, Lamping KG Understanding the coronary circulation at the microvascular level *Circulation* 1990; 82 1–7
19 Billingham ME Cardiac transplant atherosclerosis *Transplant Proc* 1987,4(suppl 5) 19–25
20 Schroeder JS, Hunt SA Chest pain in heart transplant patients *N Engl J Med* 1991;324 1805–6
21 Kountz SL, Williams MA, Williams PL, Kapros C, Dempster WJ Mechanism of rejection of homotransplanted kidneys. *Nature* 1963,199 257–99
22 Zusman DR, Stinson EB, Oyer PE, Baldwin JC, Jamieson SW, McGregor CG, *et al.* Determinants of accelerated graft atherosclerosis (AGAS) in conventional and cyclosporine treated heart transplant recipients [Abstract] *J Heart Transplant* 1985;4:587
23 Narrod J, Kormos R, Armitage J, Hardesty R, Ladowski J, Griffith B. Acute rejection and coronary artery disease in long-term survivors of heart transplantation. *J Heart Transplant* 1989,8:418–20
24 Hammond EH, Yowell RL, Nunoda S, *et al* Vascular (humoral) rejection in heart transplantation pathologic observations and clinical implications. *J Heart Transplant* 1989,8 430–43
25 Ratkovec RM, Wray RB, Renlund DG, O'Connell JB, Bristow MR, Gay WA, *et al* Influence of corticosteroid-free maintenance immunosuppression on allograft coronary artery disease after cardiac transplantation *J Thorac Cardiovasc Surg* 1990,100 6–12
26 Stamler JS, Vaughan DE, Rudd MA, *et al* Frequency of hypercholesterolaemia after cardiac transplantation *Am J Cardiol* 1988,62.1268–72
27 Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis *JAMA* 1989,261 3561–6.
28 Nitenberg A, Tavolaro O, Loisance D, Foult JM, Benhaiem N, Cachera JP Severe impairment of coronary reserve during rejection in patients with orthotopic heart transplant *Circulation* 1989,79·59–65
29 Treasure CB, Vita JA, Ganz P, Mudge GH, Alexander RW, Selwyn AP, Fish RD Small vessel coronary artery disease in cardiac transplant patients [Abstract] *J Am Coll Cardiol* 1990,2 126.
30 Wijngaard PL, de Bresser JM, De Groot PG, Gmelig-Meyling FH, Schuurman HJ, Jambroes G, Borleffs JC Endothelial and smooth muscle cells in the heart allograft response· isolation procedure and immunocytochemical features *Journal of Heart and Lung Transplantation* 1990, 10:416–23
31 Kahan BD Cyclosporine *N Eng J Med* 1990;321·1725–38
32 Scott JP, Higenbottam TW Adverse reactions and interactions of cyclosporin. *Medical Toxicology* 1988,3 107–27
33 Nitenberg A, Tavaloro O, Loisance DY, Foult JM, Cachera JP Dynamic evaluation of the coronary circulation in human orthotopic heart transplants *Transplant Proc* 1987,5:3772–6
34 McGinn AL, Wilson RF, Olivari MT, Homans DC, White CW. Coronary vasodilator reserve after human orthotopic cardiac transplantation *Circulation* 1988;78 1200–9
35 Hoffman JJ Coronary Flow Reserve In Yacoub M, ed. *Annual Of Cardiac Surgery Current Science* 1989, 90–6.
36 McKillop JH, McDougall IR, Goris ML, Mason JW, Reitz BA Failure to diagnose cardiac transplant rejection with Tc-99m PYP images *Clin Nucl Med* 1981;6 375–7

Br Heart J 1992;68:272–5

Nuclear magnetic resonance spectroscopy of excised human hearts

F Brunotte, B Peiffert, J M Escanye, G Pinelli, J Zamorano, P M Walker, J Robert, J P Villemot

Laboratoire de Biophysique, Nancy, France
F Brunotte
J M Escanye
P M Walker
J Robert

Chirurgie cardiaque Hôpital de Brabois Rue de Morvan, Vandoeuvre, France
B Peiffert
G Pinelli
J Zamorano
J P Villemot

Correspondence to
Dr F Brunotte,
Laboratoire de Biophysique,
Faculté de médecine,
21033 Dijon cedex, France

Accepted for publication
18 November 1991

Abstract

***Background*—Phosphorus nuclear magnetic resonance spectroscopy has been proposed as a method of studying the metabolism of the myocardium in patients. Little is known about ^{31}P nuclear magnetic resonance spectroscopy of diseased human hearts.**

***Methods*—Two donor hearts meeting the requirements for heart transplantation and 11 diseased hearts were removed during a transplantation procedure and were studied in a horizontal 2·35 T superconducting magnet. Spectra were obtained at 0°C about 30 minutes after the excision. The areas of the inorganic phosphate peak (Pi) and of the phosphocreatine peak (PCr) were summed and expressed as a ratio with respect to the area of the β ATP peak.**

***Results*—The ratio (Pi + PCr)/β ATP was found to be significantly lower in five hearts with a myocardial infarct (0·77 (0·18)) than in hearts with dilated cardiomyopathy (1·25 (0·29)) and in normal hearts (1·69 (0·11)). The area of the phosphodiester peak was expressed as a ratio with respect to the area of the β ATP peak: no differences were found between the three groups.**

***Conclusions*—These results suggest that the phosphocreatine concentration is lower in ischaemic heart disease than in dilated cardiomyopathy and that the phosphodiester peak is probably not useful in distinguishing between these two types of heart disease.**

(*Br Heart J* 1992;68:272–5)

Our knowledge of the energetics of failing human myocardium is limited. Magnetic resonance spectroscopy proved useful for studying the metabolism of isolated perfused hearts.[1] In recently published studies, localised phosphorus nuclear magnetic resonance spectroscopy has been used to measure myocardial high energy phosphates and phosphorylated lipids in vivo.[2-4] Results obtained by this method should be interpreted cautiously since a contamination of spectra by contributions from the blood or from the chest wall muscles is commonplace. Using magnetic resonance spectroscopy we have assessed donor and recipient hearts in a programme of heart transplantation. In such in vitro conditions the whole heart can be studied without contributions from the chest wall or blood.

Patients and methods

PATIENTS

In eleven patients undergoing a heart transplantation the heart was arrested by a cardioplegic medium and excised. All recipients were in class IV of the New York Heart Association at the time of the transplantation: one patient had valve disease, five had dilated cardiomyopathy with a mean (SD) systolic pulmonary artery pressure 47 (10) mm Hg and an ejection fraction 22·4 (6·9)%, five patients had three vessel coronary artery disease at coronary arteriography with a previous myocardial infarct with a mean systolic pulmonary artery pressure 53·9 (14·2) mm Hg (non-significant) and an ejection fraction of 24·8 (8·1)%. We also studied the hearts of two patients meeting the criteria of heart donor.

EXCISION OF THE HEARTS

The donor and recipient hearts were examined in the same manner. The cardioplegic medium had the following composition: Na^{+} 147 mmol/l, K^{+} 20 mmol/l, Ca^{++} 2 mmol/l, Mg^{++} 16 mmol/l, Cl^{-} 203 mmol/l. Cardioplegic arrest was obtained by infusing 2 litres of this solution into the aortic root. The hearts were removed and placed in two sterile plastic bags and in a plastic container filled with ice. All the hearts were studied between 15 and 30 minutes after excision. Depending on the availability of the magnet some of the hearts were studied several times.

NUCLEAR MAGNETIC RESONANCE SPECTRA ACQUISITION AND PROCESSING

Spectra were acquired in a 2·35 T, 40 cm bore, horizontal superconducting magnet (Biospec BNT100 spectrometer, Brüker, Germany). The 5 cm diameter surface coil could be tuned to both the ^{1}H (100·425 MHz) and ^{31}P (40·65 MHz) frequencies with the aid of tune/match circuits. The heart was maintained within its sterile container and positioned directly upon the coil. The field homogeneity was optimised by shimming on the proton signal; 128 free induction decays were accumulated over 2 minutes with a repetition time of 1·25 s. The radiofrequency pulse length was 70 μs and this corresponds to

Nuclear magnetic resonance indices measured in 13 hearts at different times after excision (N, normal hearts; valve, valve disease; DCM, dilated cardiomyopathy; MI, hearts post myocardial infarction).

Time after excision (h)	*Pi/PCr*	*PCr/ATP*	*(PCr + Pi)/ATP*	*PDE/ATP*	*pH*
N:					
0·5	0·18	1·49	1·77	0·11	7·5
9	9·04	0·19	1·98	0	6·6
N:					
0·5	0·15	1·42	1·62	0·21	7·3
Valve					
1	0·61	0·72	1·14	0·17	7·3
3	1·45	0·52	1·30	0·18	7·3
DCM:					
0·5	0·32	0·78	0·96	0·35	7·3
DCM:					
0·5	0·45	0·84	1·21	0·12	7·3
1	0·92	0·49	0·94	0·18	7·1
2	2·48	0·29	1·01	0·25	7·0
3	7·28	0·11	0·92	0·36	6·8
9	—	0·0	1·04	0·0	—
DCM:					
0·5	1·50	0·65	1·61	0·060	7·2
1	1·35	0·65	1·55	0·29	7·2
6	1·98	0·66	1·99	0·26	7·1
DCM:					
0·5	0·23	1·21	1·48	0·062	7·5
1	0·54	0·69	1·05	0·016	7·3
DCM:					
0·5	0·73	0·56	0·97	0·035	7·3
1	0·59	1·14	1·82	0·21	7·2
2	1·59	0·44	1·13	0·49	7·0
3	2·3	0·39	1·27	0·40	6·9
4	7·8	0·14	1·25	0·32	6·8
MI:					
0·5	1·48	0·27	0·68	0·082	7·1
MI:					
0·5	1·01	0·22	0·43	0·43	7·1
1	3·08	0·12	0·87	0·040	7·0
MI:					
0·5	0·33	0·65	0·87	0	7·4
1	0·53	0·65	0·99	0	7·2
2	0·94	0·48	0·94	0·31	7·1
3	3·96	0·25	1·21	0·29	6·8
4	7·38	0·12	1·00	0·21	6·6
MI:					
0·5	1·28	0·39	0·90	0·22	7·1
1	2·65	0·25	0·92	0·26	7·1
2	4·63	0·22	1·27	0·27	7·0
9	—	0·0	1·30	0·0	—
MI:					
0·5	0·41	0·69	0·97	0·18	7·6
1	0·92	0·57	1·09	0·14	7·5
2	1·11	0·45	0·96	0	7·2

the maximum of signal for a repetition time of 1·25 s. The total acquisition time was kept down to 5 minutes. The free induction decays were processed by conventional trapezoidal multiplication followed by a 15 Hz line broadening. The data were subsequently Fourier transformed and phase corrected to the zero and first order. The areas of inorganic phosphate (Pi), phosphocreatine (PCr), phosphodiesters (PDE), and β ATP were measured by fitting lorentzian line shapes. The individual peak areas were corrected for T1 saturation effects by comparison with a reference spectrum acquired with a repetition time of 20 s. The chemical shift of phosphocreatine with respect to the inorganic phosphates was measured to give indirect information on pH by means of the following equation: $\text{pH} = 6\cdot75 + \text{Log}\ ((d - 3\cdot27)/5\cdot69 - d))$, where d = chemical shift in ppm.[5]

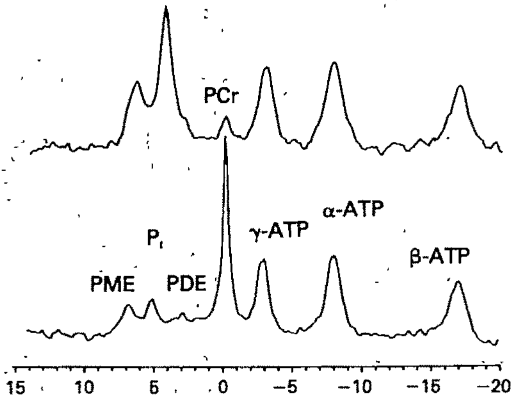


Figure 1 Spectra obtained from a donor heart studied 30 minutes after excision (bottom) and nine hours after excision (top). PME, phosphomonoester; Pi, inorganic phosphates; PCr, phosphocreatine.

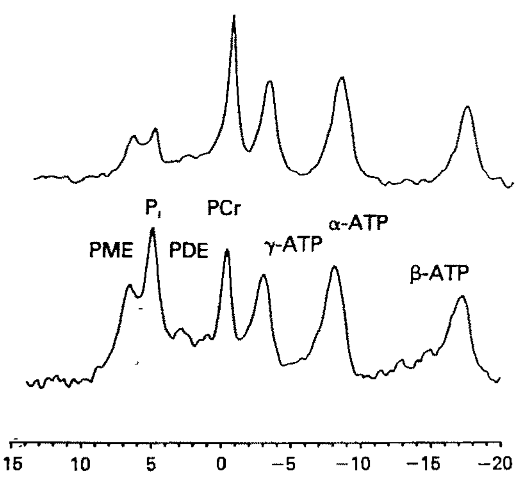


Figure 2 Spectra obtained 30 minutes after excision from two different recipient hearts with idiopathic cardiomyopathy. The ratio of the sum of inorganic phosphates and phosphocreatine to ATP was similar to that of donor hearts.

STATISTICAL METHODS

The results were expressed as mean (SD). Means were compared by Student's *t* test.

Results

The results are expressed for each heart as the ratio of phosphocreatine to β ATP (PCr/ATP), the ratio of inorganic phosphate to β ATP (Pi/ATP), the ratio of phosphocreatine plus inorganic phosphate to β ATP, and the pH (table).

Typical spectra are shown for three groups: normal hearts (fig 1), dilated cardiomyopathy (fig 2), and myocardial infarction (fig 3).

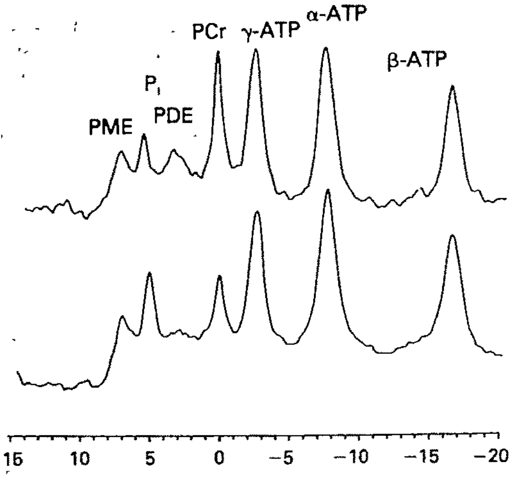


Figure 3 Spectra obtained 30 minutes after excision from two recipient hearts with coronary artery disease. The phosphocreatine concentration was low and this finding was not explained by a simultaneous increase in inorganic phosphates caused by breakdown of PCr because the sum of these two compounds remained low in comparison to ATP.

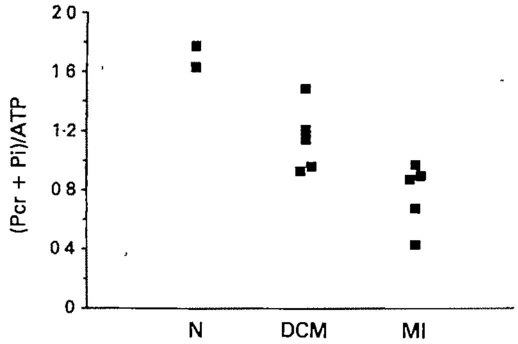


Figure 4 (PCr + Pi)/ATP ratio calculated in three groups: donor hearts (N); dilated cardiomyopathy (DCM); (myocardial infarction (MI).

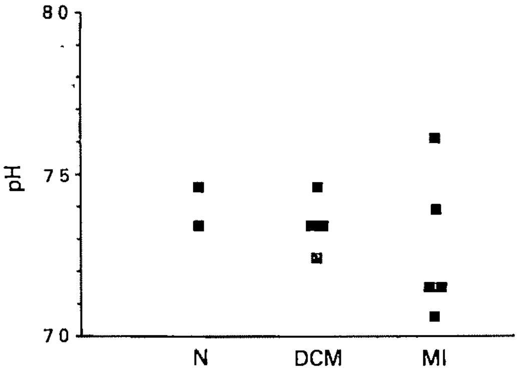


Figure 6 pH calculated in donor (N), dilated cardiomyopathy (DCM), and myocardial infarction (MI) groups.

Pi/ATP increased and PCr/ATP decreased in the hours after the excision (table) whereas the ratio (PCr + Pi)/ATP remained stable. The PDE/ATP ratio varied without any noticeable trend. The pH became more and more acidic until the PCr disappeared and the pH could not be measured. Thirty minutes after the excision (PCr + Pi)/ATP was 1·69 (0·11) in normal hearts, 1·25 (0·29) in dilated cardiomyopathy (NS), and 0·77 (0·22) in myocardial infarct ($p < 0·01$ v normal hearts and $p < 0·05$ v dilated cardiomyopathy)(fig 4). No significant difference was found for the PDE/ATP ratio (fig 5): 0·16 (0·07) in normal hearts, 0·125 (0·13) in dilated cardiomyopathy and 0·18 (0·16) in myocardial infarction. There was no difference in pH between the three groups (fig 6) (7·4 (0·1) in normal hearts, 7·3 (0·1) in dilated cardiomyopathy, and 7·3 (0·2) in myocardial infarction).

Discussion

Our study confirms that examination of whole excised human hearts by magnetic resonance spectroscopy is feasible with a wide bore horizontal magnet. Inorganic phosphates and phosphocreatine cannot be analysed separately in our study because during the cardioplegia and the first minutes of conservation breakdown of phosphocreatine is highly variable. The sum of phosphocreatine and inorganic phosphates gives an indication of the maximum amount of phosphocreatine in the heart at excision. We expressed the result as a ratio to β ATP because ATP values remain constant when phosphocreatine is still detectable. The lack of a significant change in the ratio (PCr + Pi)/β ATP during the initial hours after excision, despite the breakdown of phosphocreatine, is indirect evidence that this assumption is correct.

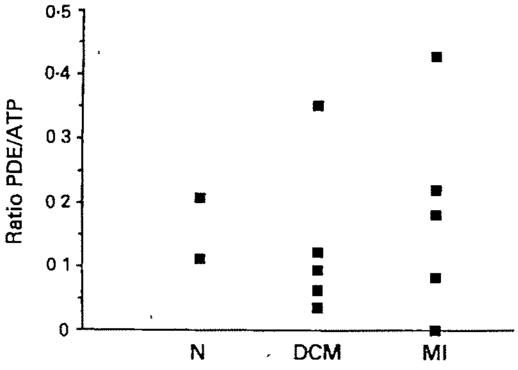


Figure 5 PDE/ATP ratio in donor (N), dilated cardiomyopathy (DCM), and myocardial infarction (MI) groups.

In the two normal hearts the (PCr + Pi)/β ATP ratio was 1·69—that is, in the same range as the ratio PCr/ATP measured in open chest pig in vivo.[6] In the perfused guinea-pig heart this ratio was about 1·8.[1] It seems likely that the normal PCr/ATP ratio in human hearts measured by nuclear magnetic resonance would be similar to the ratio in these two species. In one normal heart phosphocreatine was still detectable nine hours after excision. This suggested that the heart might still have been viable. This accords with previous findings by Van Echteld *et al*[3] and suggests that the rate of decrease of phosphocreatine in excised human heart is much slower than in hearts from small animals.

With competent technical support and adequate instrumentation a heart graft can be quickly examined. But nuclear magnetic resonance study of heart grafts cannot be recommended for two reasons: there are no reliable experimental or clinical data to show that magnetic resonance spectroscopy could predict the haemodynamic viability of the graft. Because the graft can be conserved only for a limited time the surgical procedure must be underway in the recipient when the graft arrives and the study in the magnet could delay the transplantation itself. Nevertheless, the development of techniques that allow the heart to be conserved for more than six hours could make nuclear magnetic resonance spectroscopy a useful adjunct for deciding whether the heart is viable for transplantation.

Because we studied recipient hearts under the same conditions as normal hearts, the differences we saw cannot be explained by differences in the temperature, time after excision, or nuclear magnetic resonance measurement techniques. In the failing heart, the (PCr + Pi)/ATP ratio is significantly lower in infarcted hearts, but can be nearly normal in dilated cardiomyopathy even at the terminal stage of heart failure when a heart transplant is required. Differences between hearts with myocardial infarction and dilated cardiomyopathy cannot be explained by different ejection fractions or pulmonary artery pressures. In isolated perfused rat hearts the ratio PCr/ATP reflected the imbalance between metabolic demand and energy supply which led to a reduction of the percentage of creatine that is phosphorylated.[1] It could be argued that a partial volume effect from the scar and the surrounding jeopardised myocardium could modify the measurements in a heterogeneous myocardium but it is unlikely that this effect could modify results expressed as a ratio of phosphocreatine to ATP. Another hypothesis is that the concentration of the total creatine falls. Such a fall was seen in human myocardium with hypertrophy caused by aortic stenosis and in the myocardium of patients with coronary artery disease.[7] The reduced PCr/ATP ratio in ischaemic heart diseases could reflect a metabolic adaptation either to the hypertrophy of the non-infarcted area or to the ischaemia induced by the coronary artery disease itself. Further studies are needed to clarify these issues.

Myocardial pH calculated by the classic formula was rather alkaline. This is due to hypothermia.[8] Use of another pH titration curve ($pH = 6{\cdot}88 + \text{Log}\ (d - 3{\cdot}35)/5{\cdot}6 - d)$) established at 4°C[9] would have led to even more alkaline pH values. Any attempt to correct for these effects of temperature would induce a parallel modification of the calculated pH in all the studied hearts and no intergroup significant differences would appear, suggesting that the pH is not modified even in severe heart diseases.

We found no difference in the concentration of phosphodiesters between the different groups we studied. Phosphodiesters have an NMR frequency between inorganic phosphates and phosphocreatine. They are regarded as being a consequence of muscle modifications both in myocardium[10] and in skeletal muscle.[11] The fact that the hearts were studied with a minimum quantity of blood after the infusion of the cardioplegic medium suggests that in some cases the reported PDE peak during in vivo studies could have been related to a partial volume effect of blood. Our data suggest that phosphodiesters do not aid the identification of different types of myocardial disease.

Our data provide information on the phosphorus spectroscopy findings in normal and diseased hearts and should contribute to a better understanding of the spectra obtained in vivo. Further work is needed to explain the observed decrease of the PCr/ATP ratio in ischaemic hearts.

We thank Professor G K Radda, Dr B Rajagopalan, and Dr AM Seymour for helpful discussions.

1 Brooks WM, Haseler LJ, Clarke K, Willis RJ. Relation between the phosphocreatine to ATP ratio determined by ^{31}P nuclear magnetic resonance spectroscopy and left ventricular function in underperfused guinea-pig heart. *J Mol Cell Cardiol* 1986,18 149–55.

2 Hardy CJ, Weiss RG, Bottomley PA, Gerstenblith G, Chackov P Localized phosphorus 31 nuclear magnetic resonance spectroscopy in humans with dilated cardiomyopathy. Society of Magnetic Resonance in Medicine. 8th annual meeting. August 1989. Amsterdam, p 509.

3 Van Echteld CJA, Kirkels JH, Jambroes G, Kodde JH, Lahpor JR, Ruigrok TJC. Human donor heart preservation assessed by ^{31}P nuclear magnetic resonance spectroscopy. Society of Magnetic Resonance in Medicine. 8th annual meeting. August 1989. Amsterdam, p 512

4 Rajagopalan B, Blackledge MJ, McKenna WJ, Bolas N, Radda GK. Measurement of phosphocreatine to ATP ratio in normal and diseased human heart by ^{31}P magnetic resonance spectroscopy using the rotating frame-depth selection technique. *Ann NY Acad Sci* 1987,508 321–32

5 Taylor DJ, Bore RJ, Styles P, Gadian DG, Radda GK. Bioenergetics of intact human muscle a 31-P nuclear magnetic resonance study *Mol Biol Med* 1983,1:77–94

6 Rajagopalan B, Bristow JD, Radda GK Measurement of transmural distribution of phosphorus metabolites in the pig heart by ^{31}P magnetic resonance spectroscopy. *Cardiovasc Res* 1989,23:1015–26.

7 Ingwall JS, Kramer MF, Fifer MA, Lorell BH, Shemin R, Grossman W, Allen PD The creatine kinase system in normal and diseased human myocardium. *N Engl J Med* 1985,313 1050–54.

8 White FN. A comparative physiological approach to hypothermia *J Thorac Cardiovasc Surg* 1988,82 821–31

9 English TA, Foreman J, Gadian DG, Pegg DE, Wheeldon D, Williams SR Three solutions for preservation of the rabbit heart at 0°C. A comparison with phosphorus-31 nuclear magnetic resonance spectroscopy *J Thorac Cardiovasc Surg* 1988;96 54–61.

10 Shaefer S, Schwartz GG, Gober JR, Meyerhoff DJ, Weiner MW, Massie B. ^{31}P spectroscopic imaging of global myocardial disease: elevation of phosphodiesters in patients with left ventricular dilation [abstract] *Circulation* 1989,80 588

11 Burt CT, Pluskal MG, Streter FA. Generation of phosphodiesters during fast to slow muscle transformation. A ^{31}P Nuclear magnetic resonance study *Biochem Biophys Acta* 1982;721·492–4.

Br Heart J 1992;68:276–81

Intravascular ultrasound imaging of the coronary arteries: an in vitro evaluation of measurement of area of the lumen and atheroma characterisation

Mark H Anderson, Iain A Simpson, Demosthenes Katritsis, Michael J Davies,
David E Ward

Abstract

***Objective*—To assess the accuracy of measurement of area of the lumen, and sensitivity, and specificity of detection of atheroma in coronary arteries in vitro with a commercially available 20 MHz intravascular ultrasound system.**

***Setting*—A teaching hospital department of cardiology with the support of the department of cardiovascular pathology.**

***Procedure*—10 segments of coronary artery were removed from cadaver hearts. Intravascular ultrasound imaging was performed at fixed levels and the vessels were then sectioned and photographed before histological preparation. An independent blinded observer measured luminal area and assessed the presence of atheroma on the intravascular ultrasound images of 76 vessel sections (304 quadrants). The sensitivity and specificity of detection of atheroma was assessed in comparison with the histologically prepared sections. Luminal areas from intravascular ultrasound, photographs of cross sections of the vessels and histological sections were compared with the technique of limits of agreement.**

***Results*—Overall 36% of the 304 quadrants studied histologically had identifiable atheroma. Intravascular ultrasound sensitivity for atheroma was 0·593 and the specificity was 0·839. The positive predictive value was 0·674, and the relative risk 3·139. Values for area of the vessel lumen were on average 9·4 mm^2 (confidence interval (CI) 8·6–10·2 mm^2) larger than those measured from photographs and 10·7 (CI 9·8–11·6 mm^2) larger than those measured from the histological sections.**

***Conclusions*—The intravascular ultrasound system assessed in this study significantly overestimated coronary vessel luminal area and had low sensitivity and specificity for detection of atheroma. Improvements in image resolution are required before this system can provide useful information on coronary artery size and morphology.**

(*Br Heart J* 1992;48:276–81)

Department of Cardiological Sciences, St George's Hospital Medical School, London
M H Anderson
I A Simpson
D Katritsis
D E Ward

British Heart Foundation Cardiovascular Pathology Unit, St George's Hospital Medical School, London
M J Davies

Correspondence to
Dr M H Anderson,
Department of Cardiological Sciences, St George's Hospital Medical School,
London SW17 0RE.

Accepted for publication
12 March 1992

The concept of imaging the coronary arteries from within the lumen with ultrasound is not new but early attempts were limited by catheter technology.[1] The development over the last 15 years of intravascular interventional procedures such as angioplasty and atherectomy has renewed interest in intravascular imaging. The realisation that the distribution and structure of the atheromatous plaque are important factors affecting the success of these strategies spurred interest in intravascular ultrasound and angioscopy. Imaging of the vessel after the intervention would enable assessment of the response of the atheroma to the treatment and identification of features associated with satisfactory long-term outcome. Although angioscopy can achieve imaging in front of the catheter tip it provides information on surface appearance only whereas intravascular ultrasound has the potential advantage of providing information on the deeper composition of the vessel wall including atheromatous plaques. This tantalising prospect is responsible for the current explosion of interest in intravascular ultrasound techniques.

Recently published studies have shown excellent correlation of vessel measurements made by ultrasound with those obtained at angiography[2] and by histological studies in vitro.[3] Also some studies have suggested that detailed information about the composition of the plaque may be obtained.[4] The goal of our study was to see whether we could match the promising results suggested by these clinical studies with a commercially available ultrasound system, when applied in vitro to coronary artery specimens. Specifically we aimed to assess the accuracy of luminal area measurements made by the system and its ability to identify plaque morphology when compared with histological examination.

Method

SPECIMEN PREPARATION

Ten hearts with a short length of ascending aorta and the coronary sinuses intact were removed from cadavers at post mortem examination. A piece of plastic tubing was placed in the aorta and elastic bands ensured a snug waterproof connection between the tube and the aorta. Fixative solution (10% formaldehyde) was perfused into the aorta at a pres-

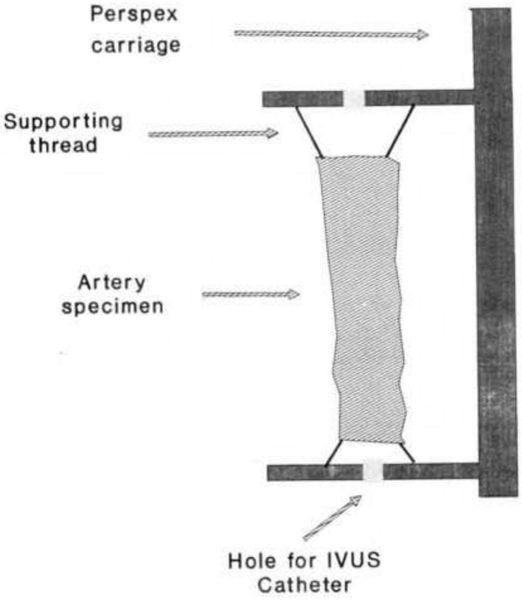


Figure 1 Coronary artery specimen sutured in Perspex carrier.

sure of 100 mm Hg to simulate systemic pressure. The fixative drained into a lower reservoir from which it was recycled by a pump. After 24 hours connected to this system the heart was removed and a two cm long segment of coronary artery (nine hearts) or aortocoronary bypass graft (one heart) was removed for further study. This pressure fixation technique is used to maintain arterial morphology during subsequent processing.

Excess fat was dissected away from the segment of artery. The artery was suspended within the limbs of a Perspex carrier with 6° prolene (fig 1). Sutures were adjusted so that the specimen was central but not under tension.

A Diasonics intravascular ultrasound system that provided the images ws connected to a 4·8 French gauge 20 MHz ultrasound imaging catheter (Sonicath^{TM}, Boston Scientific Instruments). This catheter has a monorail tip to enable passage over a guide wire. Of necessity the ultrasound transducer was positioned some 3 cm back from the tip (fig 2). Before use the tip of this catheter was filled with sterile degassed water through a seal located within the monorail port in accordance with the manufacturer's instructions. The tip was then swung gently by hand to displace any small bubbles over the transducer. The proximal end of the catheter attaches to a motor drive unit which in turn is attached by flexible cable to the Diasonics ultrasound machine. The machine displays the image from the catheter on a six inch screen. Gain and magnification are variable. For both we used the settings recommended in the manufacturer's manual and these remained unchanged throughout the study. An on line facility allows measurement of circumference and area of outlines traced on the screen.

After preparation of the ultrasound imaging catheter the Perspex carriage supporting the artery specimen was placed in a small jig. The jig includes a water bath that was filled before addition of the carriage. A stainless steel screw mechanism enables the artery carriage to be raised or lowered precisely. The ultrasound imaging catheter was then placed into the water bath, passing through a small hole in the top of the artery carriage, down through the lumen of the artery, and through another small hole in the bottom of the carriage to finish with the tip just touching the bottom of the water bath (fig 3). The imaging catheter was supported so that it formed a smooth curve on its way to connect with the drive motor. For ease of manipulation the guide wire was omitted during this study.

EXPERIMENTAL PROTOCOL

The Perspex carriage supporting the artery specimen was slowly raised until an ultrasound image of the top of the specimen was just visible. Starting 2 mm from the top of each piece of artery, ultrasound images were taken at 3 mm intervals. The images were recorded on video tape and the luminal area was traced

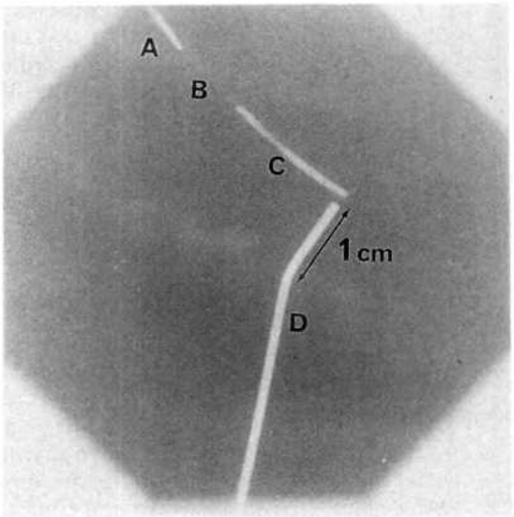


Figure 2 x Ray appearance of the ultrasound imaging catheter tip. (A) Ultrasound transducer; (B) fluid filled space; (C) radiopaque catheter tip; (D) metal marker probe.

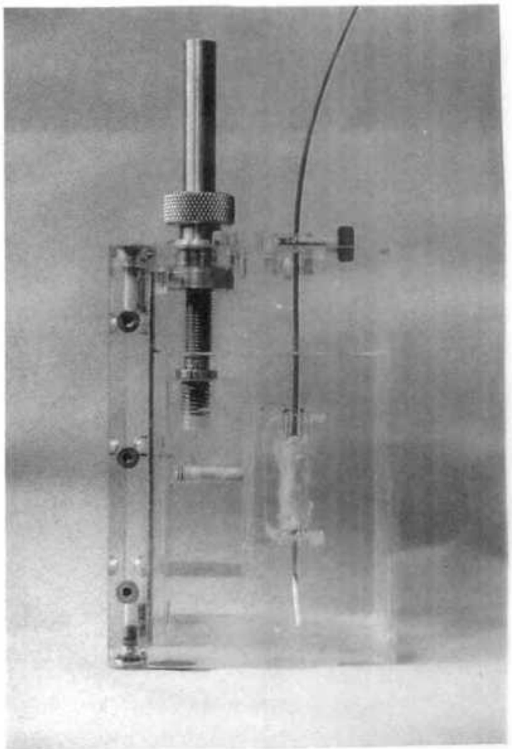


Figure 3 Jig with specimen carriage in place and ultrasound imaging catheter passing through specimen.

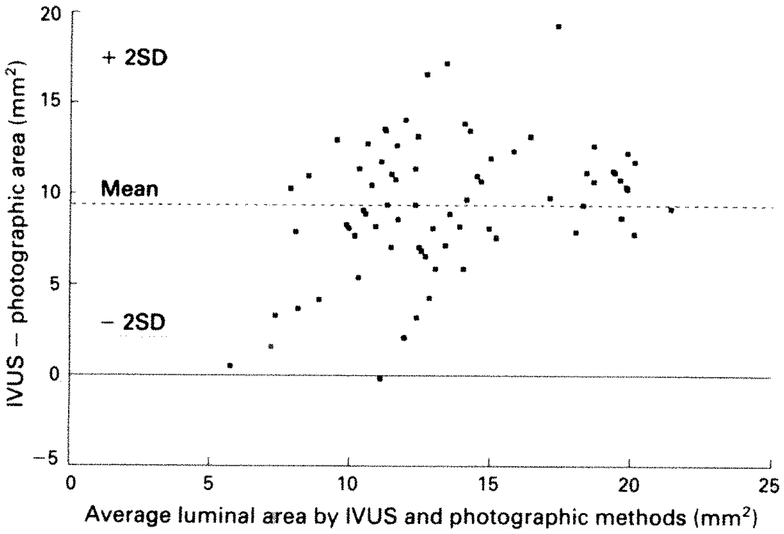


Figure 4 Difference between luminal area measured by the intravascular ultrasound system and that measured from photographs of vessel sections plotted against the mean of the two values. Fixed lines show the mean of the difference and 2 SD from this mean.

round by hand and measured by the Diasonics ultrasound machine. The image was orientated by placing a fine needle in front of the anterior wall of the artery before the first image. On completion of collection of the images the artery carriage was removed from the water bath. A fine line was drawn down the anterior wall of the artery with indelible ink and the upper end of the specimen was marked. The sutures were removed. The artery was then transferred to a shaped cutting block that supported the tissue while a multibladed cutter sliced it at levels that corresponded to the ultrasound images. The 3 mm segments that corresponded to each ultrasound image were photographed with the cut surface corresponding to the ultrasound image uppermost, with a small plastic block of known size for calibration. The area of the lumen was measured from the photographs with a digitising tablet and Apple Macintosh SE computer. Each specimen was then embedded in paraffin wax and histological sections were made that corresponded to the ultrasound images. The histological slides were examined through an AMS quantifying microscope with video planimetry to measure the luminal area. On inspection the section was divided into four quadrants—from 45° to 135°, 135° to 225°, 225° to 315°, and from 315° to 45°. The presence or absence of atheroma and calcification was recorded for each segment by an independent observer. With the images recorded on videotape a similar procedure by another investigator was repeated for the ultrasound images by comparing each quadrant with adjacent quadrants and also adjacent segments. The luminal areas and qualitative judgements on the presence or absence of atheroma in the ultrasound, photographic, and histological images were compared.

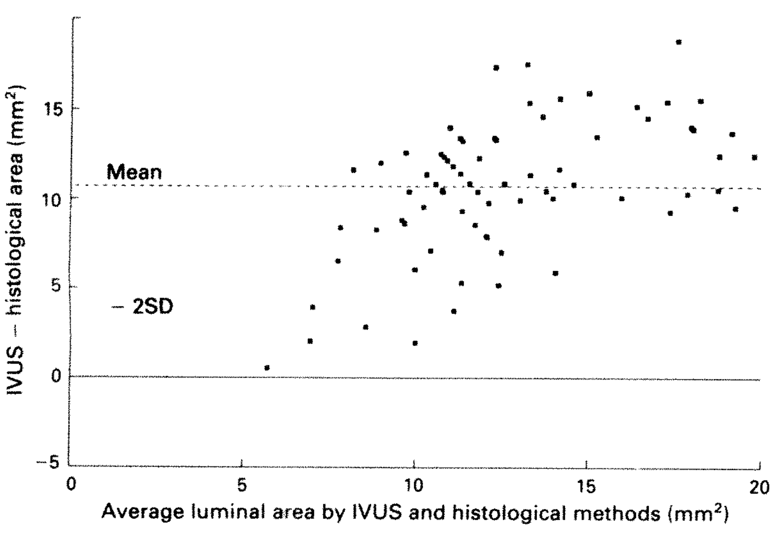


Figure 5 Difference between luminal area measured by the intravascular ultrasound system and that measured by microscopy of vessel sections plotted against the mean of the two values. Fixed lines show the mean of the difference and 2 SD from this mean.

For calibration two sections of polyethylene tube of known size (4·1 and 5·4 mm internal diameter) were placed on the artery carriage and their lumens were imaged and measured. The measurement was repeated five times for each tube.

STATISTICAL ANALYSIS

The measurements of luminal area taken from each method were compared with the method of limits of agreement[5] to assess measurement bias and confidence intervals. The presence or absence of atheroma on histological examination was used to assess the sensitivity and specificity of the observations made from the ultrasound images.

A probability value of $p < 0{\cdot}05$ was considered statistically significant and confidence intervals were calculated as mean (2 SD) with 75 degrees of freedom.

Results

Figure 4 shows the results of a comparison of area of the vessel lumen measured by ultrasound and by photography of the vessel sections. Values of the area measured by ultrasound were on average 9·39 mm^2 larger than the same area measured from photographs of the vessel slices (confidence intervals (CI) for an individual ultrasound area measurement was 2·10–16·7 mm^2 > photographic area, CI for the mean difference was 8·6–10·2 mm^2). A similar pattern was noted when measurements of area by ultrasound were compared with those made by the AMS quantifying microscope (fig 5). The ultrasound area was on average 10·7 mm^2 greater than that measured histologically (CI for an individual ultrasound area 3·2–18·2 mm^2 > histological area, CI for the mean difference 9·8–11·6 mm^2). By contrast (fig 6) there was close agreement between the histological and photographic techniques (mean difference −1·3 mm^2, CI of an individual histological area measurement −4·3 to +1·6 mm^2 compared with the photographic area, CI for the mean difference −1·6 to −0·97 mm^2). The overestimation of area of the lumen by the intravascular ultrasound system in relation to the other two techniques was statistically and clinically significant. The wide

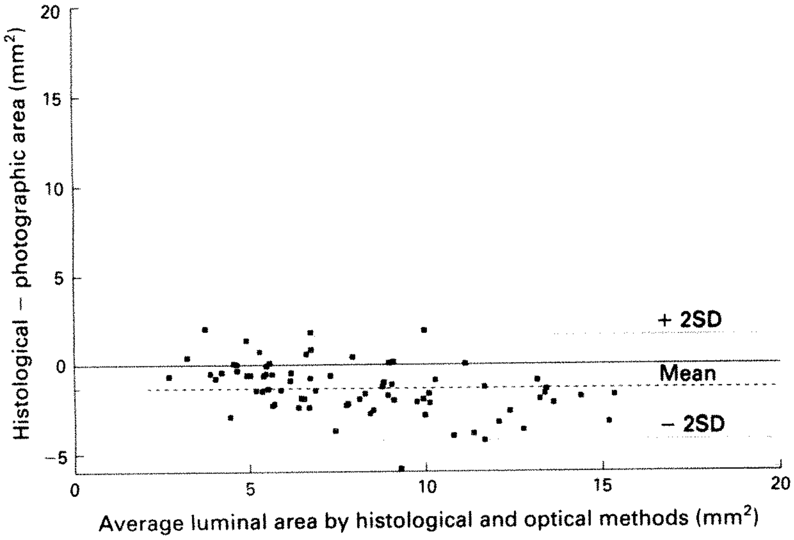


Figure 6 Difference between luminal area measured by microscopy of vessel sections and that measured from photographs (optical) of the sections plotted against the mean of the two values.

CI for luminal area measurements made with the ultrasound system also reduces its value. Interestingly the intravascular ultrasound system showed a much reduced bias when measuring the lumen of polyethylene tubes of known diameter (fig 7). Areas measured by ultrasound were only 2·14 mm^2 greater than the actual area calculated from the mean of the two diameters measured by micrometer (CI for an individual measurement 0·22–4·06 mm^2, CI for the mean difference 1·53–2·75 mm^2). Eccentric positioning of the ultrasound imaging catheter within the polyethylene tube had little effect on the measured values.

The presence or absence of atheroma detected by ultrasound and histological examinations was compared. Overall 36% of the 304 quadrants studies had identifiable atheroma on histological examination. Ultrasound sensitivity was 0·593 and the specificity was 0·839. The positive predictive value was 0·674, and the relative risk 3·139.

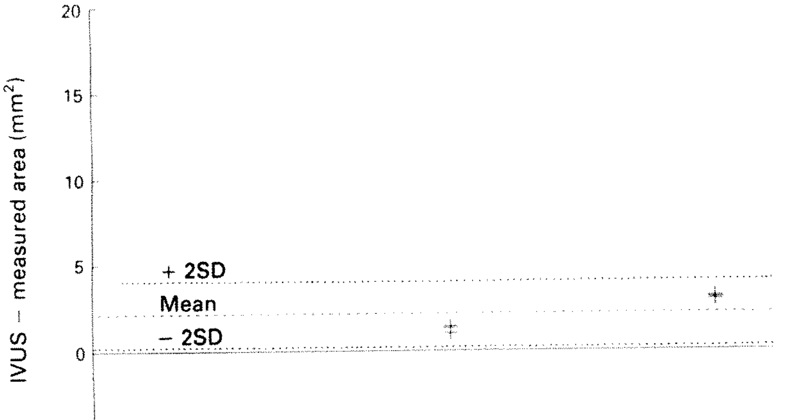


Figure 7 Difference between luminal area measured by the intravascular ultrasound system and the measured diameter of polyethylene tubes plotted against the mean of the two values. Fixed lines show the mean of the difference and 2 SD from this mean.

Discussion

The development of transcoronary treatments such as angioplasty, atherectomy, rotary ablation, and stent placement has led to a growth of interest in the internal morphology of the coronary arteries. The precise morphology of atheroma and its constitution may be important factors in determining the initial success rate of stenosis after these procedures.[6] Interpretation of coronary angiography is subjective and a poor correlation between angiographic and post mortem pathological findings has been shown.[7 8] Interest has centred on whether intravascular ultrasound can offer more accurate information on size of the lumen and atheroma morphology. Some studies have provided conflicting answers to this question.

With a 25 MHz catheter Potkin and colleagues[9] studied fixed and unfixed specimens of coronary artery and compared the luminal areas with those measured after histological fixation. They found a correlation coefficient $r = 0·85$ (luminal area by ultrasound $= 1·13 \times$ lumenal area by histology $-0·58$). Mean luminal area was 2·65 mm^2. Gussenhoven *et al*[10] used a 40 MHz catheter to study peripheral arteries before histological fixation and sectioning. Ultrasound measurements correlated closely with histological measurements ($r = 0·847$) but the gradient of the relation diverged considerably from unity (ultrasound $= 0·587 \times$ histology $+11·8$). Mean luminal area was 25 mm^2.

Similarly variable results have been reported for the comparison of ultrasound luminal areas with those derived from angiography. Davidson *et al*[11] reported a high degree of correlation ($r = 0·95$) between luminal areas derived from ultrasound and digital subtraction angiograms in peripheral vessels, and another study reported good results ($r = 0·80$) in the coronary vessels although the luminal areas measured by ultrasound were on average 35% larger than those derived by angiography.[12] Tobis *et al*[13] reported a correlation coefficient of only 0·26 between ultrasound and angiographic measurements of the lumen in areas of vessels apparently normal by angiography.

The results of our study show a poor level of agreement between ultrasound measurements and cross sectional areas measured from scaled photographs and histological specimens. By contrast the photographic and histological measurements show close agreement. The measurements made by the photographic technique were individually calibrated reducing the risk of significant error. The only processing performed between ultrasound imaging and photographic measurements was sectioning of the specimens. Distortion of the specimens after sectioning was not seen reflecting the firm texture of the vessel after pressure fixation. The small difference between the areas measured from photographs and those taken from histological sections is probably due to shrinkage occurring during histological processing of the specimens.

The intravascular ultrasound system was calibrated with polyethylene tubing of known internal diameter. Ultrasound luminal area

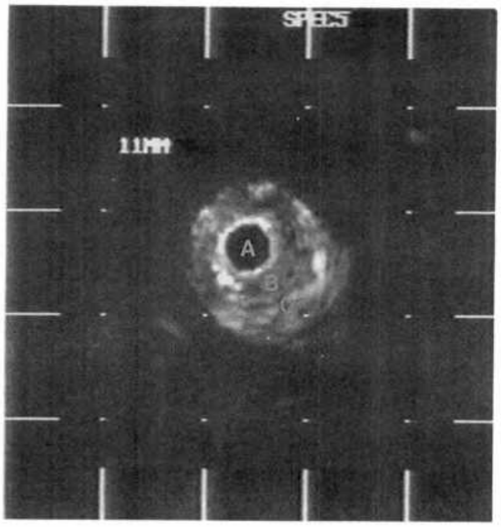


Figure 8 Typical intravascular ultrasound image. The dark central shadow (A) is surrounded by a bright pericatheter halo. More distant vessel wall structure is clearly seen (C) but the exact boundary between lumen and intima is impossible to identify (B).

only slightly overestimated measured area with a difference in mean (CI) of 2·14 (1·53–2·75) mm^2. Axial tilting of the catheter within the artery specimen could account for a small overestimate of area. The length (2 cm) of our arterial specimens, however, and the close support provided for the imaging catheter by the imaging jig make this explanation unlikely. Another possible explanation for the discrepancy in measurements of area of the lumen is the use of saline rather than blood in the immersion bath. Moriuchi *et al*[14] have considered this question in detail. They showed a small (6%) increase in cross sectional area of measurements performed in saline rather than blood. Whereas this would not account for the large discrepancy in our measurements of ultrasound area made in coronary vessels it might account for the overestimation (roughly 10%) of the area of the polyethylene tubes by the intravascular ultrasound system. Other groups have also shown that the use of saline in the specimen bath is unlikely to be a major source of error in measurement of luminal area.[15]

There appears to be a fundamental difference in the error in measurement of luminal area when the intravascular ultrasound system is used in coronary arteries compared with polyethylene tubes. During interpretation of the coronary artery ultrasound images great difficulty was often encountered in finding the precise location of the boundary between the lumen and the intima, and the boundary was sometimes obscured by the near field ring shadows originating from the catheter itself (fig 8). It is likely that poor definition of this boundary and hence overestimation of the area of the vessel lumen explains the large bias noted. In the polyethylene tubes a very sharp image of the boundary between lumen and tubing was produced with more accurate measurement of luminal area.

Our original intention was to grade the appearance of the ultrasound images as previously defined.[4] On the basis of peripheral vascular studies bright echoes with shadows behind indicate calcium deposits, bright echoes alone indicate collagen rich fibrous tissue, soft echoes indicate fibromuscular tissue, intimal proliferation, and diffuse lipid, whereas hypoechoic areas indicate significant pooling of lipid. Unfortunately the quality of the images that we obtained was not consistently good enough to make a classification. In view of this difficulty we compared each ultrasound and histological image quadrant by quadrant for the presence or absence of atheroma (each scored by an independent observer). Atheroma was defined on the ultrasound images as thickening of the vessel wall associated with one or more of the appearances defined above. Histological definition of atheroma excluded simple intimal thickening. Histological examination showed atheroma in 36% of the 304 quadrants examined.

Not surprisingly in view of the difficulty with identification of the luminal border and substructure of the vessel wall, sensitivity of the ultrasound technique for atheroma was low (0·593), although with somewhat better specificity (0·839).

Despite numerous reports indicating that intravascular ultrasound is a more sensitive detector of atheroma within the coronary arteries than angiography,[16 17] there have been no formal studies comparing its sensitivity with histological examination of the vessel. Those studies that have shown excellent correlation have used peripheral arteries with larger lumens and thicker walls.[4 13] These peripheral vessels tend to produce superior ultrasound images.

POSSIBLE EXPLANATIONS OF THE DISCREPANCY BETWEEN THE ULTRASOUND AND HISTOLOGICAL DATA

The primary factor limiting the accuracy of measurement of luminal area and identification of atheroma in this study seems to be the quality of the ultrasound image and failure to identify the interface betwen lumen and intima. When a clear interface occurred as in the polyethylene tubes the system appears to measure the luminal area accurately. Several factors could be responsible for the reduced quality of image.

Single transducer catheters such as the one in this study use a rotating drive shaft to turn the transducer itself (as in this catheter) or an ultrasound mirror to reflect the signal from a fixed transducer. Both types of catheter are subject to non-uniform rotational distortion due to the limited torsional rigidity of the drive shaft.[18] In other words the tip of the drive shaft may lag behind the motor drive unit by angles of up to 40° depending on angle of the catheter and speed of rotation. This lag may vary during the course of each rotation due to the "slip and stick" phenomenon and this in turn can produce apparent compression or expansion of segments of the artery wall. The 4·8 F catheter in this study is one of the smallest catheters used for such imaging studies and may be more prone to lack of torsional rigidity in the drive shaft for this reason. Such problems could account for some of the variability in measurements of the luminal area and discrepancies in the localisation of atheroma.

One feature of the images produced by this catheter was the pericatheter near field effect that often obscured the exact junction between the lumen and the intima when the catheter was positioned close to the vessel wall (fig 8). This effect may be less troublesome in catheters with a rotating mirror rather than a rotating transducer. In this type of catheter the near field of the transducer falls partly or wholly within the distance between the transducer and the mirror and therefore is not apparent on the processed image of the vessel wall.[19] The 4·8 F catheter used in this study must have its tip filled with sterile water before use and the inclusion of air bubbles at this stage can cause degradation of the image. The catheter tip was, however, carefully filled in accordance with the manufacturer's instructions and there was no evidence of bubble artefact on the images produced.

The small size of this catheter may contribute to the difficulty of getting a clear image. As catheter size is reduced, the aperture of the transducer element is also reduced accentuating lateral resolution artefacts.[20] This may produce a smearing of the image particularly at interfaces between atheromatous plaques and the normal arterial wall.

It is important to consider whether the formalin pressure fixation technique used for the arterial specimens could alter the quality of the ultrasound images and thus account for some of the difficulties we found. It is known that formalin fixation can increase the strength of the reflected ultrasound signal.[21] Tobis *et al*[22] however, showed only a small change in luminal area measured by ultrasound after formalin fixation and made no comment concerning any change in the appearance of the vessel. Also the pressure fixation technique may have some benefits. There has been much discussion about the three layered appearance of intravascular ultrasound images of muscular arteries that has been noted by some authors[4 23] but not by others.[24 25] Such differences may reflect differences in preparation of the specimens. The appearance of an inner ring on intravascular ultrasound images is exaggerated in non-pressure fixed specimens. This may be due to contraction and corrugation of the internal elastic lamina.[26] The technique of pressure fixation that we have used is, we think, most likely to retain the morphology and qualitative ultrasound features of the artery specimens when compared with in vivo arteries.

Although 20 MHz single transducer probes can produce excellent images in the peripheral vessels the results of our study would suggest that further improvements in catheter design are required to get clinically useful images of the coronary arteries. A number of approaches may improve the quality of the images from such catheters. A higher ultrasound frequency enables improved resolution albeit with some loss of penetration. Increasingly, images systems for coronary imaging catheters use ultrasound frequencies in the 30–50 MHz range. The use of an array of ultrasound crystals in place of a single crystal offers an alternative means of improving image quality. Computer processing of the image may enable the effective focal length of such a transducer to be varied.

In conclusion the intravascular ultrasound system evaluated in our study lacks the ability to produce accurate information on the dimensions and morphology of medium sized coronary arteries although the system is reported to produce excellent images of larger peripheral arteries. Further technical developents are required before this system can produce useful images of the coronary arteries in vivo.

We are grateful to Diasonics UK for the loan of the ultrasound machine and to the Medical Physics department at St George's Hospital for their assistance with construction of the specimen jig and cutter

1 Bom N, ten Hoff H, Lancée CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices *Int J Card Imaging* 1989,4:79–88.

2 Nissen SE, Grines CL, Gurley JC, *et al*. Application of a new phased-array ultrasound imaging catheter in the assessment of vascular dimensions. *Circulation* 1990,81.660–6.

3 Panadian NG, Kreis A, O'Donnell T Intravascular ultrasound estimation of arterial stenosis. *J Am Soc Echocardiogr* 1989,2 390–7.

4 Gussenhoven WJ, Essed CE, Frietman P, *et al* Intravascular echographic assessment of vessel wall characteristics: a correlation with histology. *Int J Card Imaging* 1989;4 105–16.

5 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i 307–10.

6 Liu MW, Roubin GS, King SB. Restenosis after coronary angioplasty *Circulation* 1989,79:1374–87.

7 De Rouen T, Murray JA, Owen W. Variability in the analysis of coronary arteriograms *Circulation* 1977, 55:324–8.

8 Grondin CM, Dyrda I, Pasternac A, Campeau L, Bourassa MG, Lesperance J. Discrepancies between cineangiographic and postmortem findings in patients with coronary artery disease and recent myocardial revascularisation. *Circulation* 1974;49 703–8

9 Potkin BN, Bartorelli AL, Gessert JM, *et al* Coronary artery imaging with intravascular high-frequency ultrasound *Circulation* 1990;81·1575–85

10 Gussenhoven EJ, Essed CE, Lancee CT, *et al* Arterial wall characteristics determined by intravascular ultrasound imaging: an in vitro study *J Am Coll Cardiol* 1989,14: 947–52.

11 Davidson CJ, Sheikh KH, Harrison K, *et al*. Intravascular ultrasound versus digital subtraction angiography· a human in vivo comparison of vessel size and morphology [abstract]. *J Am Coll Cardiol* 1990;15.16.

12 Nissen SE, Gurley JC, Booth DC. In vivo assessment of human coronary minimum luminal diameter with a multielement intravascular ultrasound catheter comparison to quantitative cineangiography [abstract] *J Am Coll Cardiol* 1990,15·29

13 Tobis JM, Mallery J, Mahon D, *et al*. Intravascular ultrasound imaging of human coronary arteries in vivo. *Circulation* 1991,83.913–26.

14 Moriuchi M, Tobis JM, Mahon D, *et al* The reproducibility of intravascular ultrasound imaging in vitro. *J Am Soc Echocardiogr* 1990,3·444–50.

15 Hodgson J McB, Graham SP, Savakus AD, *et al* Clinical percutaneous imaging of coronary anatomy using an over-the-wire ultrasound catheter system. *Int J Cardiac Imaging* 1989;4:187–93.

16 Keren G, Douek P, Hansch E, Milner MR, Pichard AD, Leon MB Intravascular ultrasound characteristics of atheroma in angiographically "normal" segments [abstract] *J Am Coll Cardiol* 1991,17:217.

17 Tobis JM, Mahon D, Lehmann K, McRae M, Henry WL. The sensitivity of ultrasound imaging compared with angiography for diagnosing coronary atherosclerosis [abstract]. *Circulation* 1990,82 439.

18 ten Hoff H, Korbijn A, Smit TH, Klinkhammer JFF, Bom N. Imaging artefacts in mechanically driven ultrasound catheters *Int J Card Imaging* 1989;4 195–9.

19 Mallery JA, Tobis JM, Griffith J, *et al*. Assessment of normal and atherosclerotic arterial wall thickness with an intravascular ultrasound imaging catheter. *Am Heart J* 1990,119:1392–400.

20 Crowley RJ, von Behren PL, Couvillon LA, Mai DE, Abele JE Optimized ultrasound imaging catheters for use in the vascular system *Int J Card Imaging* 1989,4·145–51

21 Gussenhoven EJ, Essed CE, Lanceé CT, *et al* Arterial wall characteristics determined by ultrasound imaging an in vitro study *J Am Coll Cardiol* 1989,14 947–52

22 Tobis JM, Mallery JA, Gessert J, *et al*. Intravascular ultrasound cross-sectional imaging before and after balloon angioplasty in vitro *Circulation* 1989;80 873–82.

23 Pandian NG, Kreis A, Weintraub A, *et al*. Real-time intravascular ultrasound imaging in humans. *Am J Cardiol* 1990,65·1392–6.

24 Gurley JC, Nissen SE, Diaz C, Fischer C, O'Connor WN, DeMaria AN. Is the tri-layer arterial appearance an artefact? Differences between in vivo and in vitro intravascular ultrasound [abstract]. *J Am Coll Cardiol* 1991;17 112.

25 Fitzgerald PJ, St Goar FG, Kao AK, *et al*. Intravascular ultrasound imaging of coronary arteries: is three layers the norm? [abstract]. *J Am Coll Cardiol* 1991;17.217.

26 Webb JG, Yock PG, Slepian MJ, *et al*. Intravascular ultrasound. significance of the three-layered appearance of normal muscular arteries [abstract]. *J Am Coll Cardiol* 1990,15:17

Br Heart J 1992;68:282–5

Lower threshold for adenosine-induced chest pain in patients with angina and normal coronary angiograms

Bo Lagerqvist, Christer Sylvén, Anders Waldenström

Abstract

***Objective*—To investigate whether patients with angina-like chest pain and normal coronary angiograms are more sensitive to adenosine as an inducer of chest pain.**

***Design*—Increasing doses of adenosine were given in a single blind study as intravenous bolus injections. Chest pain and the electrocardiographic findings were noted.**

***Patients*—Eight patients with angina-like chest pain but no coronary stenoses (group A), nine patients with angina and coronary stenoses (group B), and 16 healthy volunteers (group C).**

***Results*—In the absence of ischaemic signs on the electrocardiogram adenosine provoked angina-like pain in all patients in groups A and B. The pain was located in the chest, and its quality and location were described as being no different from the patient's habitual angina. In group C, 14 of 16 subjects reported chest pain. The lowest dose resulting in chest pain was lower in group A (0·9 (0·6) mg) than in group B (3·1 (1·5) mg) ($p < 0{\cdot}005$) and in group C (6·2 (3·7) mg) ($p < 0{\cdot}005$). The maximum tolerable dose was lower in group A (4·7 (2·1) mg) than in group B (9·2 (3·8) mg) ($p < 0{\cdot}05$) and in group C (12·0 (4·1) mg) ($p < 0{\cdot}005$).**

***Conclusions*—Patients with angina-like chest pain and normal coronary angiograms have a low pain threshold and low tolerance to pain induced by adenosine.**

(*Br Heart J* 1992;68:282–5)

Department of Internal Medicine, University Hospital, Uppsala, Sweden
B Lagerqvist
A Waldenstrom

Department of Medicine, Huddinge University Hospital, Huddinge, Sweden
C Sylvén

Correspondence to
Dr Bo Lagerqvist,
Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden

Accepted for publication
24 October 1991

Despite studies on many patients with angina-like pain and normal coronary angiograms, the mechanisms of the syndrome are unclear.[1–4] The causes may be multifactorial and a decreased capacity to dilate the coronary arteries and to increase coronary blood flow in response to pharmacological provocation with dipyridamole or rapid atrial pacing has been suggested.[5 6] A lower threshold and tolerance to both ischaemic pain and electrical skin stimulation on the forearm have been reported in women with syndrome X.[7]

The links between myocardial ischaemia and chest pains are not completely clear though adenosine was proposed by Sylvén *et al* to be a metabolic messenger.[8 9] Adenosine given intravenously or directly into a coronary artery induced angina-like pains without the electrocardiographic (ECG) signs of ischaemia both in patients with ischaemic heart disease in healthy volunteers.[8 10 11] Patients with predominantly silent ischaemia tolerate higher doses of adenosine than patients with predominantly painful ischaemia.[12]

When dipyridamole is given to patients with ischaemic heart disease for the study of thallium-201 scinitigraphy or echocardiography, chest pains are reported by up to 40% of the patients. When dipyridamole was given to patients with angina pectoris and normal coronary angiograms 68–95% of the patients reported chest pains.[2 13 14] Dipyridamole has several mechanisms of action and an important one is an increased extracellular concentration of adenosine caused by the inhibition of the cellular uptake of adenosine.[15]

Because this suggested a role for adenosine we studied whether patients with angina-like pains and angiographically normal coronary arteries have a lower tolerance to adenosine as a pain inducer.

Patients and methods

PATIENTS

Group A comprised eight patients (three male) with typical effort related angina but without any stenosis on the coronary angiograms. Their mean (SD) age was 56 (13) years and mean (SD) weight 68 (7) kg. All had localised perfusion defects on thallium-201 myocardial scintigraphy at exercise with reversibility at rest. All these perfusion defects had primarily been interpreted as being of the "ischaemic type". Five of the eight patients had horizontal or down sloping ST segment depression of at least 0·1 mV and chest pains on an ergometer exercise stress test: the rest had only chest pain without any ST depression. All patients had previously been paced to pain (mean frequency 154 (22) beats/min) and three of the eight had signs of myocardial lactate production with a higher lactate concentration in coronary sinus blood than in arterial blood. Five of the patients were classified as functional group III and three as functional group II according to the New York Heart Association (NYHA) classification. No-one in group A had a previous history of myocardial infarction, hypertension, or diabetes. The results of left ventricular angiography and the echocardiography were classified as normal in all patients in group A. None of the patients showed any signs of coronary spasm during hyperventilation or a non-invasive ergometrine (ergonovine) test.[14 16]

Group B comprised nine patients (all men) with angina and coronary stenosis, (at least 50% diameter reduction) on coronary angiography. Three of them had one vessel disease, one had one vessel disease and main stem stenosis, two had two vessel disease, and three had three vessel disease. A previous myocardial infarction had been clinically diagnosed in four of the patients. Four of them were treated for hypertension. All of the patients were classified as belonging to NYHA functional group III. Their mean age was 58 (6) years and mean weight was 78 (8) kg.

Group C was a control group of 16 healthy volunteers (six men) aged 43 (8) years and with a mean weight of 68 (11) kg. None of them had any history or symptoms suggesting heart disease.

All antianginal medication was stopped and the subjects were told to abstain from xanthine-containing food and drinks for at least 12 hours before the experiment. No other premedication was given except 3 g amoxycillin and 15 mg oxazepam to those who were catheterised to measure coronary sinus blood flow at the same time.

The study was approved by the local ethics committee. The background and the procedure were thoroughly explained to the subjects before consent was obtained.

PROCEDURE

The sterile solution of adenosine (5·3 mg/ml, Janssen) was prepared by the hospital pharmacy. In a single blind manner adenosine or saline was injected rapidly as a bolus injection into an antebrachial vein. After each dose the vein was flushed with 5 ml saline. The initial dose was 2·5 mg adenosine. Based on the pain response the dose was increased or decreased in small steps in order to reach the "highest dose not giving pain" and the "lowest dose giving pain". The adenosine dose was changed in a single blind manner in irregular steps and adenosine was alternated with injections of saline. The dose was thereafter increased step by step until the subject refused a further increase, ST depression was seen on the electrocardiogram, or an atrioventricular block II-III occurred. This dose was defined as the "maximum dose". The dose intervals were lower for low doses and higher when higher doses were given. Doses of adenosine between 0·1 and 15 mg were given. The next dose was given 3–5 minutes after the disappearance of pain or other symptoms caused by the previous dose.

At the onset of pain the patient raised his or her left hand, when the maximum pain began to subside the hand was lowered half way, and when the pains had disappeared the hand was lowered to the supine position. These time points were noted on the online recording of the electrocardiogram (V1–V6) (25 mm/s). The magnitude of maximal pain was rated according to a category-ratio scale designed to quantify perceptual intensities, the Borg CR-10 scale.[17] The patient was also asked to describe the location and the character of the pain, especially with respect to differences from and similarities to his/her experience of angina.

In five patients in group A and five patients in group B a coronary sinus flow catheter (Wilton-Webster, USA) was introduced via the right internal jugular vein into the coronary sinus under fluoroscopic control. The position was tested by injection of contrast medium. The coronary sinus blood flow was determined by the thermodilution technique.[18]

STATISTICAL ANALYSIS

Values are expressed as means (SD) unless otherwise stated. We used the Kruskal-Wallis test for analysis of variance, the Mann-Whitney U test for intergroup differences between unpaired samples, and the Wilcoxon signed rank test to test for statistical heterogeneity between paired samples.

Results

In the absence of ischaemic electrocardiographic signs injection of adenosine into a peripheral vein induced pain in all patients in groups A and B. The pain was mainly located in the chest and was described as being the same as the patient's habitual angina in quality and location. In group C intravenous injection of adenosine resulted in chest pain in 14 of 16 subjects. In two of the subjects the dose was not increased because an atrioventricular block occurred before any chest pain was noted.

Table 1 and fig 1 summarise the pain reactions to adenosine injection. The highest dose not giving pains, the lowest dose giving pains, the maximum dose of adenosine were lower in group A than in group B and in group C. These differences were all statistically significant ($p < 0·05$) and the differences in threshold remained when differences in body weight were accounted for. The pain appeared earlier ($p < 0·005$) and lasted longer ($p < 0·001$) after

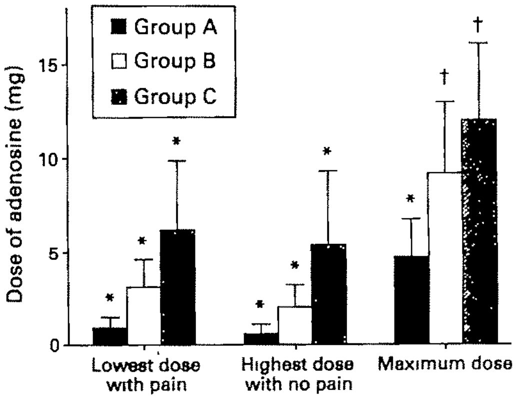


Figure 1 Lowest dose of adenosine provoking pain, highest dose not giving pain, and maximum dose when adenosine was injected intravenously in the different groups of patients. Analysis of the variance was by the Kruskal-Wallis test and localisation of intergroup differences by the Mann-Whitney U test.
**Different from the other two groups ($p < 0·05$); †different from group A ($p < 0·05$)*

Table 1 Highest dose of adenosine not giving pains, lowest dose giving pains, maximum dose, degree of pain according to Borg CR-10 scale at maximum dose of adenosine, time from injection to start of pain, and duration of pain when adenosine was injected intravenously into the different groups of patients

	Group A (n = 8)	*Group B (n = 9)*	*Group C (n = 16)*	*Analysis of variance p value*
Highest dose not giving pains (mg)	0·6 (0·5)*	2·0 (1·2)*	5·4 (3·9)*	<0·001
Lowest dose giving pains (mg)	0·9 (0·6)*	3·1 (1·5)*	6·2 (3·7)*	<0·001
Maximum dose (mg)	4·7 (2·1)*	9·2 (3·8)†	12·0 (4·1)†	<0·001
Pain degree at maximum dose (Borg CR-10)	7·4 (1·5)	6·2 (1·9)	4·5 (2·3)†	<0·01
Time to pain at lowest dose giving pain (s)	20 (5)	22 (5)	20 (7)	>0·2
Pain duration at lowest dose giving pain (s)	18 (10)	18 (9)	19 (16)	>0·2
Time to pain at maximum dose giving pain (s)	18 (4)	18 (5)	16 (4)	>0·2
Pain duration at maximum dose giving pain (s)	31 (10)	30 (26)	29 (15)	>0·2

Analysis of the variance by Kruskal-Wallis test and localisation of intergroup differences by Mann-Whitney U test.
*Different from the other two groups, $p < 0·05$; †different from group A, $p < 0·05$.

the maximum dose than after the lowest dose of adenosine. The degree of pain, according to the Borg CR-10 scale, was lower in group C than in group A ($p < 0·05$). Figure 2 highlights the relation between the maximum dose of adenosine given and the degree of the reported pain.

Short periods of atrioventricular block II and III developed in 15 subjects (one in group A, three in group B, and 11 in group C) and a short sinus arrest/sinoatrial block was seen in one of the subjects (group B) after adenosine injection. The longest duration of block was 5 s. The mean lowest dose of adenosine resulting in block was 10·0 (4·3) mg. The mean time from the start of the injection to the beginning of the block was 15 (4) s, and this was not statistically different from the time of injection to onset of pain (16 (4) s) in these subjects. The uneven distribution of the appearance of atrioventricular blocks could not be taken as an indication of different electrophysiological response to adenosine in the three groups because the maximum doses differed between the groups.

Table 2 shows the effect of adenosine on coronary sinus blood flow. There was no statistically significant difference between groups A and B in terms of the beginning of the increase in coronary sinus blood flow or in the time from injection to flow increase or from injection to maximum flow. Nor was there any difference in the increase of flow between the lowest dose giving pain and the maximum dose.

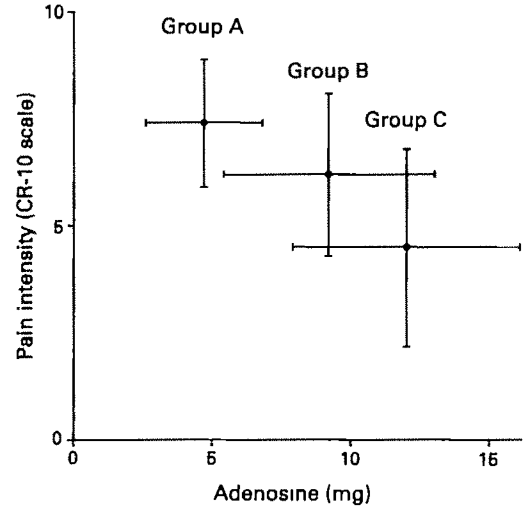


Figure 2 Relation between the maximal bolus dose of adenosine given intravenously and the degree of pain provoked according to the Borg CR-10 scale in groups A, B, and C.

When the results for all the subjects were analysed together we found that the lowest dose giving pain resulted in a coronary sinus blood flow increase that came earlier (15 (4) s) than the pain (21 (4) s, $p < 0·01$). This also occurred when the maximum dose of adenosine was injected (15 (3) s and 18 (4) s, respectively, $p < 0·01$).

Injection of saline did not result in any pain or increase in coronary sinus blood flow or lead to atrioventricular block in any of the patients.

Discussion

Both in the group with angina-like pains and normal coronary angiograms (group A) and in the group with ischaemic heart disease (group B) the pains induced by adenosine were described as being no different from the usual exercise induced chest pain. Group A was more sensitive to adenosine. This could be an expression of a generally higher sensitivity to pain of different causes or specifically to pain evoked by adenosine. Turiel *et al* found a lower threshold and a lower tolerance both to ischaemic forearm pain and to electrical skin stimulation, but not to cold in women with syndrome X than in those with stable angina and coronary stenoses.[7] Another study of a group of patients with normal coronary angiograms found that despite a higher pain sensitivity in the right side of the heart to catheter manipulations the threshold for cutaneous pain stimulation by heat was higher than in a group of patients with ischaemic heart disease.[19]

In the myocardium adenosine is produced under normal conditions and acts as a local vasodilator.[20] During ischaemia its production is greatly enhanced and it is released in large quantities into the coronary circulation.[21 22] The difference between normal physiology and ischaemia is not qualitative but quantitative—with increasing energy expenditure increasing amounts of adenosine are released.[23] Our study implies an increased sensitivity also to endogenously produced adenosine. This could explain why patients with angina without coronary stenoses report pain in the absence of signs of ischaemia such as pathologically increased exertional diastolic pulmonary artery

Table 2 Effects of adenosine on coronary sinus blood flow (CSBF) in groups A and B

	Group A *(n = 5)*	*Group B* *(n = 5)*
Increase in CSBF, as % of baseline flow, maximum dose	202 (84)	211 (94)
Time to CSBF increase at lowest dose giving pain (s)	14 (2)	16 (5)
Time to CSBF maximum at lowest dose giving pain (s)	22 (2)	27 (7)
Time to CSBF increase at maximum dose of adenosine (s)	14 (1)	15 (5)
Time to CSBF maximum at maximum dose of adenosine (s)	23 (3)	25 (5)

pressure[24] or such as hypokinesia during the dipyridamole echocardiography test.[13] It is not known whether or not myocardial ischaemia is the main cause of chest pains in this group of patients. The exercise induced chest pains in these patients are not necessarily caused by ischaemia. It is possible that this group of patients has pain at adenosine concentrations that are lower than those caused by ischaemia, or that they have raised resting concentrations of adenosine that are nearer the threshold concentration for pain.

This study does not exclude an extracardiac origin for the adenosine induced pain, but a cardiac origin is the most likely. In patients with ischaemic heart disease both intravenous and intracoronary bolus doses of adenosine result in the same kind of angina-like chest pains.[10] Chest pains were not produced when adenosine was given as an infusion into the right atrium at the same dose that provoked pain when given directly into a coronary artery.[12] Further evidence is provided by the fact that when adenosine was given intravenously to patients with heart transplants the pain threshold was greatly increased.[25]

The difference in sensitivity between the group with ischaemic heart disease and healthy volunteers has not been described before. This could reflect a true difference or it could be the result of the experimental design. Five patients in each of groups A and B were more intensively investigated with invasive monitoring of coronary sinus blood flow and these patients were also premedicated with oxazepam. It is possible that a subjective index such as pain could be influenced by a difference in experimental design such as this. However, this is unlikely because healthy volunteers investigated by coronary sinus catheterisation without premedication reported similar intensities of chest pain to those seen in group C after intravenous bolus doses of adenosine.[26] Another explanation could be that the patients in groups A and B were all selected because they had chest pain, whereas patients with silent angina may have been recruited from a separate subgroup. We do not know how many of the subjects in group C might have belonged to this subgroup.

In conclusion, in both patient groups intravenous bolus doses of adenosine provoked chest pain that was no different from their habitual angina. Patients with normal coronary angiograms showed a lower tolerance than patients with coronary stenoses and healthy volunteers. These observations might add to the understanding of patients with angina-like pain but normal coronary angiograms.

This study was supported by grants from the Swedish Heart and Lung Foundation and from Josef and Linnea Carlsson Foundation

1 Cannon RO, Bonow RO, Bacharach SL, *et al* Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries, and abnormal vasodilator reserve. *Circulation* 1985,71·218–26.

2 Cannon RO, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988,61 1338–43.

3 Greenberg MA, Grose RM, Neuburger N, Silverman R, Strain JE, Cohen MV. Impaired coronary vasodilator responsiveness as a cause of lactate production during pacing-induced ischemia in patients with angina pectoris and normal coronary arteries *J Am Coll Cardiol* 1987; 9:743–51.

4 Camici PG, Marraccini P, Lorenzoni, R, *et al* Coronary hemodynamics and myocardial metabolism in patients with syndrome X: Response to pacing stress. *J Am Coll Cardiol* 1991;17:1461–70.

5 Opherk D, Zebe H, Weihe E, *et al*. Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms *Circulation* 1981,4·817–25

6 Cannon RO, Watson RM, Rosing DR, Epstein SE Angina caused by reduced vasodilator reserve of the small coronary arteries *J Am Coll Cardiol* 1983;1·1359–73

7 Turiel M, Galassi AR, Glazier JJ, Kaski JC, Maseri A. Pain threshold and tolerance in women with syndrome X and women with stable angina pectoris *Am J Cardiol* 1987; 60 503–7

8 Sylvén C, Beermann B, Jonzon B, Brandt A Angina pectoris-like pain provoked by intravenous adenosine in healthy volunteers *Br Med J* 1986,293:227–30.

9 Sylvén C. Angina pectoris. Clinical characteristics, neurophysiological and molecular mechanisms. *Pain* 1989, 36:145–67.

10 Lagerqvist B, Sylvén C, Beermann B, Helmius G, Waldenstrom A. Intracoronary adenosine causes angina pectoris like pain—an inquiry into the nature of visceral pain. *Cardiovasc Res* 1990,24.609–13.

11 Lagerqvist B, Sylvén C, Hedenstrom H, Waldenstrom A Intravenous adenosine but not its first metabolite inosine provokes chest pain in healthy volunteers *J Cardiovasc Pharmacol* 1990,16.173–6.

12 Crea F, Pupita G, Galassi AR, *et al*. Role of adenosine in pathogenesis of anginal pain. *Circulation* 1990,81 164–72.

13 Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. Usefulness of a high-dose dipyridamole-echocardiography test for diagnosis of Syndrome X. *Am J Cardiol* 1987,60:508–12.

14 Lagerqvist B, Bylund H, Götell P, Mannting F, Sandhagen B, Waldenstrom A. Coronary artery vaso-regulation and left ventricular function in patients with angina pectoris-like pain and normal coronary angiograms *J Int Med* 1991;230 55–65.

15 Roos H, Pfleger K. Kinetics of adenosine uptake by erythrocytes, and the influence of dipyridamole. *Mol Pharmacol* 1972;8·417–25

16 Ginsburg R, Lamb IH, Bristow MR, Schroeder JS, Harrison DC. Application and safety of outpatient ergonovine testing in accurately detecting coronary spasm in patients with possible variant angina. *Am Heart J* 1981, 102:698–702.

17 Borg G. A category scale with ratio properties for intermodal and interindividual comparisons. In: Geissler H-G, Petzold P, eds Psychophysical judgement and the progress of perception. Berlin VEB Deutscher Verlag der Wissenschaften, 1982;25–34

18 Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC Measurement of coronary sinus blood flow by continuous thermodilution in man *Circulation* 1971,44. 181–95.

19 Cannon RO, Quyyumi AA, Schenke WH, *et al* Abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries. *J Am Coll Cardiol* 1990;16 1359–66.

20 Berne RM, Cardiac nucleotides in hypoxia· Possible role in regulation of coronary blood flow. *Am J Physiol* 1963, 204.317–22

21 Bardenheuer H, Hofling B, Fabry A, Peter K. Increased adenosine production by the heart during acute coronary occlusion ins man. *Anesthesiology* 1097;67.311

22 Okazaki Y, Hirayama A, Sato H, Kitakaze M, Kodama K. Adenosine release during exercise accounts for warm-up phenomenon at 2nd exercise. *Circulation* 1990;82: III–444.

23 Edlund A, Fredholm BB, Patrinani P, Patrono C, Wennmalm A, Wennmalm M. Release of two vasodilators—adenosine and prostacyclin—from isolated rabbit hearts during controlled hypoxia. *J Physiol* 1983,340:487–501.

24 Levy RD, Shapiro LM, Wright C, Mockus L, Fox KM Syndrome X: the haemodynamic significance of ST segment depression *Br Heart J* 1986,56·353–7.

25 Lagerqvist B, Sylvén C, Helmius G, Waldenstrom A. Effects of exogenous adenosine in a patient with transplanted heart. Evidence for adenosine as a messenger in angina pectoris *Ups J Med Sci* 1990,95 137–45.

26 Sylvén C, Jonzon B, Edlund A Angina pectoris-like pain provoked by i v bolus of adenosine· relationship to coronary sinus blood flow, heart rate and blood pressure in healthy volunteers *Eur Heart J* 1989;10 48–54

Br Heart J 1992;68:286–90

Detection of myocardial ischaemia by transthoracic leads in ambulatory electrocardiographic monitoring

Christian M Jespersen, Verner Rasmussen

Holter Laboratory, Hvidovre Hospital, Hvidovre, Denmark
C M Jespersen
V Rasmussen

Correspondence to
Dr C M Jespersen,
Østerbrogade 82,
DK-2100 Copenhagen Ø,
Denmark.

Accepted for publication
18 November 1991

Abstract

***Objective*—To determine the best sites for ambulatory monitoring leads to detect myocardial ischaemia.**

***Patients*—50 consecutive patients recovering from myocardial infarction. Six patients were excluded because of unsatisfactory recordings or baseline electrocardiographic abnormalities that influenced the diagnostic accuracy of ST segment depression. In 38 patients important ST segment changes were seen before the study recordings.**

***Main outcome measure*—Reproducibility of detecting the electrocardiographic ST segment changes with 12 bipolar leads alone or in combination.**

***Results*—The highest reproducibility rate was found in infarcts involving both the anterior and inferior left ventricular walls (80%). The reproducibility decreased as the extent of ventricular wall involvement decreased and was lowest in inferior infarcts (31%) ($p < 0.001$). For large infarcts the detection rate was almost equal for the 12 study leads, whereas disparity between leads increased as the infarct size decreased. The highest overall reproducibility was found in a transthoracic lead (V2, V9R) (76%). This lead was significantly better ($p = 0.03$) than lead CM5 (50%). When the transthoracic lead was combined with an inferior lead, the reproducibility increased (82%) and was significantly better than the combination of CM5 and an inferior lead (58%) ($p = 0.02$).**

***Conclusions*—Extensive ischaemic electrocardiographic changes are better detected than smaller ones and anterior infarcts better than inferior. A transthoracic lead (V2, V9R) was significantly better than CM5 both alone and when CM5 and the transthoracic lead were combined with an inferior lead.**

(*Br Heart J* 1992;68:286–90)

In an earlier paper[1] we recommend a modified orthogonal y lead for detection of left ventricular inferior wall ischaemia and the CM5 lead for detection of anterior wall ischaemia. Because the diagnosis of anterior ischaemia is normally based on six precordial leads, it may be that the CM5 lead does not reliably detect small areas of ischaemia in the left ventricle. To assess the optimal sites for ambulatory leads we compared 12 different bipolar leads in patients recovering from acute myocardial infarction.

Patients and methods

Fifty patients with enzymatically confirmed myocardial infarction were consecutively included in the study. We excluded patients with unstable myocardial diseases, arrhythmias, bundle branch block, electrocardiographic indications of ventricular hypertrophy or strain or both, and patients treated with antiarrhythmic drugs or digoxin because these characteristics interfere with the interpretation of the electrocardiogram. The location of the infarct was identified by serial electrocardiographic recordings, and the infarct location was classified according to the following criteria: changes in leads II, III, aVF as inferior; in V1–V3 (V4) as septal; in V4–V6 as apical; in V6, I, and aVL as lateral; in V1–V6 (I, aVL) as extensive; and when changes were seen in both inferior and anterior walls simultaneously as combined. The type of infarction was classifed on the basis of the presence of abnormal Q waves.

The recordings were carried out before discharge, when the patients were in a stable phase. A standard 12 lead electrocardiogram was recorded immediately before the study recordings and was used as a reference. Twelve bipolar leads were studied (table 1, fig 1). Four leads (1–4) were sagittally orientated, three (5–7) were placed on the anterior aspect of the thorax, three were oblique leads (8–10), one was transversely orientated (11), and one was a modified inferior lead (12). Leads 11, 12, and 2 corresponded to the orthogonal leads x, y, and z, respectively, and lead 7 corresponded to CM5.

A segment of each lead comprising at least 200 QRS complexes was stored on a TEAC R–71 tape recorder after amplification. The recordings were analysed by a signal averaging program (HIPEC HA 100). Fifty QRS complexes with a cross correlation factor that was greater than or equal to 0·95 were included in each lead. Low and high filter cut offs were set at 40 and 250 Hz, respectively. The averaged QRS complex of each lead was plotted out on a Sweet-p plotter.

ST segment deflection was measured 80 ms after the J point and was considered to be significant (positive) if it was $\geq 0{\cdot}1$ mV.

Table 1 Position of negative and positive electrodes in the 12 experimental bipolar leads

	Negative electrode	*Positive electrode*
Sagittal leads:		
1	V9	V2
2	V3	V9
3	V9	V5
4	V9	Xiphoid process
Chest leads:		
5	Manubrium	V2
6	Manubrium	V3
7	Manubrium	V5
Oblique leads:		
8	V9R	V2
9	V9R	V3
10	V9R	V5
Transverse lead:		
11	V6R	V6
Inferior lead:		
12	Superior angle left scapula	Above the left iliac crest

STATISTICAL ANALYSIS

We used the χ^2 test with a level of significance set at $p \leq 0\cdot05$. The difference between proportions (DBP) and the 95% confidence interval (95% CI) were calculated by the CIA Statistical package, *BMJ*, England, 1990.

Results

Fifty consecutive patients with acute myocardial infarction were enrolled in the study. Six patients were excluded because of bundle branch block ($n = 3$), atrial fibrillation ($n = 1$), prior enrolment ($n = 1$), and unsatisfactory recording ($n = 1$). The total study population thus consisted of 44 patients. The infarct was inferior in 12, septal in nine, anterior in two, lateral in five, extensive in eight, and combined in eight patients. In 24 (55%) the infarct was a non-Q-wave infarct.

When the study recordings were made ST segment deflection was seen in the experimental electrocardiographic leads in 38 (86%). In six patients, two with a non-Q wave and four with a Q wave infarct, ST segment deflection had disappeared at the time of recording. Figure 2 shows the number of significant ST segment deflections in the 12 study leads according to infarct location in patients with persisting ST segment deflections in the experimental electrocardiographic leads. The two patients with apical infarcts are not shown. In these patients, however, ST segment deflections were seen in all study leads except in lead 12 in one patient. Figure 2 shows that the total number of positive recordings varied with the location of the infarct. Figure 3 shows overall frequency of positive recordings according to location of the infarct. The detection rate for combined infarcts was significantly higher than for extensive ($p = 0\cdot04$), lateral ($p = 0\cdot002$), septal ($p < 0\cdot001$), and inferior infarcts ($p < 0\cdot001$). The detection rate in patients with extensive infarcts was significantly higher than in patients with septal ($p < 0\cdot001$) and inferior infarcts ($p < 0\cdot001$) but not in patients with lateral infarcts. The detection rate in patients with lateral infarcts was significantly higher than in patients with septal ($p = 0\cdot02$) and inferior infarcts ($p = 0\cdot008$). No significant difference was found between septal and inferior infarcts.

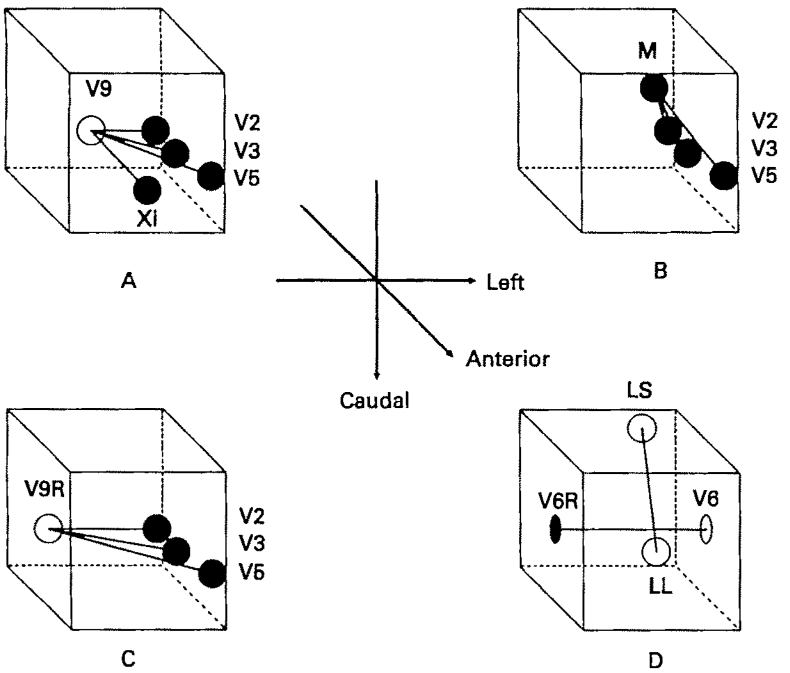


Figure 1 Spatial orientation of twelve study leads. (A) sagittal leads (1 to 4 craniocaudal direction); (B) chest leads (5 to 7 from centre to lateral); (C) oblique leads (8 to 10 craniocaudal direction); and (D) orthogonal x and y leads. LL, left iliac crest; LS, left scapula; M, manubrium; Xi, xiphoid process.

Figure 4 shows the overall detection rates of the study leads. The rate was highest for lead 8 (74%). Leads with a detection rate of 50% or less were significantly inferior to lead 8 (50%: $p = 0\cdot03$; DBP = 24%; 95% CI 3% to 45%). In five leads (1, 2, 6, 8, and 9) the detection rate exceeded 60%. In all these leads, one electrode was located at the V2 or V3 position and all the leads except one were sagittal or oblique leads. The overall detection rate in lead CM5 (lead 7) was 50% and detection rates in all leads with one electrode in the V5 position (3, 7, and 10) were 50% or less. The lowest overall detection rate (39%) was seen in the inferior lead (12). In patients with inferior infarcts lead 12 was better than CM5, but was surpassed by one sagittal (1) and one oblique lead (9) (fig 2). The combination of leads 8 and 12 gave a detection rate (82%) that was better than all other combinations. When lead 7 (CM5) was combined with lead 12 the rate was 58%, which was significantly less than leads 8 and 12 combination ($p = 0\cdot02$; DBP = 24%; 95% CI 8% to 44%). When combined with lead 12, six other leads (1, 2, 4, 5, 6, and 9) detected more ST segment deflections than the lead 7 and 12 combination, but the differences were not statistically significant. Table 2 shows different combinations of leads 7, 8, and 12 according to small (inferior, septal, lateral) and large infarcts (apical, extensive, combined). For small infarcts the combination of leads 8 and 12 was better than the 7 and 12 combination ($p = 0\cdot06$; DBP 29%; 95% CI −0% to 57%). In large infarcts, lead 8 missed only one ST segment deflection (fig 2), and no other lead increased the detection rate when combined with lead 8. Lead 7 detected 12 (71%) out of 17 possible deflections in patients with large infarcts. When lead 7 was combined with lead 12 the detection rate increased to

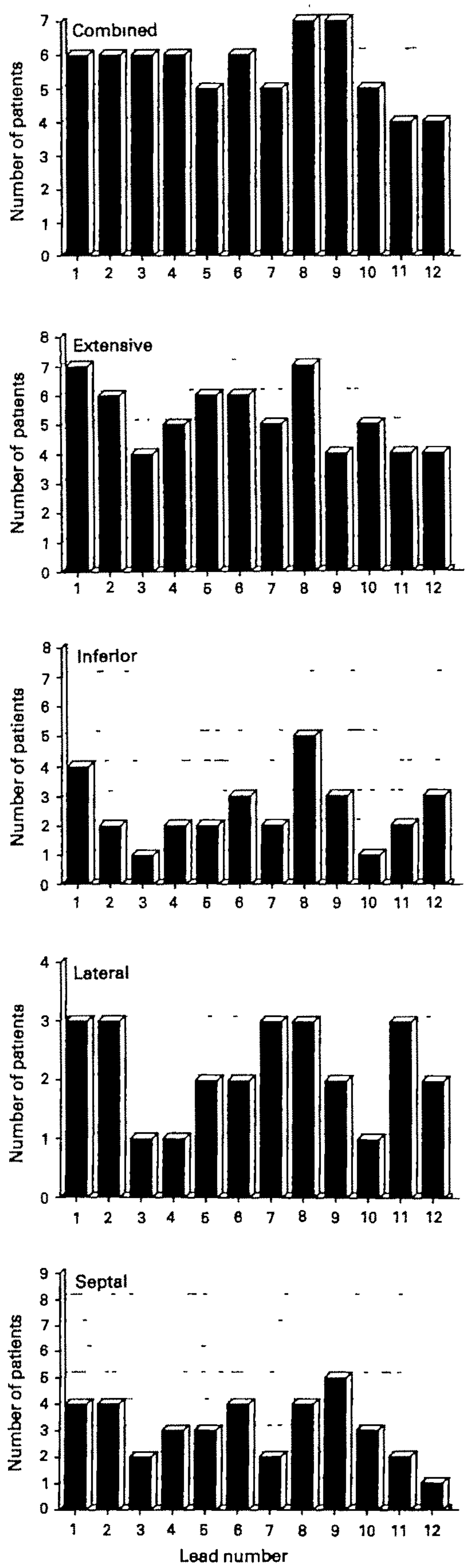


Figure 2 Number of positive recordings in 12 experimental leads according to infarct location.

76%, which was not significant different from the lead 8 and 12 combination.

All combinations detected large infarcts better than small ones. For small infarcts the 8 and 12 combination was best, detecting 71% of small infarcts and 94% of large ones (p = 0·07; DBP 0·22; 95% CI 0·00 to 0·11). When the 7 and 12 combination was used 71% of large and 43% of small infarcts were detected (p = 0·04; DBP 0·34; 95% CI 0·04 to 0·63).

In four patients no significant ST segment changes were seen in the electrocardiogram immediately before the study recordings. In one of these patients study leads 1, 2, 8, 9 showed a significant displacement. In two patients with serial electrocardiographically verified inferior Q wave infarcts no ST segment changes were seen in the inferior leads in the standard electrocardiogram. In these patients persistent significant ST segment depression was seen in leads V1–V3 and significant changes were found in study leads 1 and 8 and 1, 2, 4, 5, 7, 8, 9, and 11 respectively.

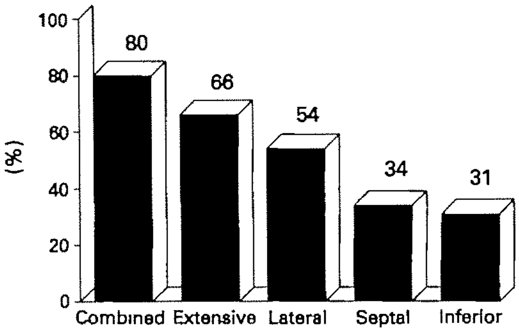


Figure 3 Frequency of significant ST segment deviations in experimental leads according to location of infarct.

Discussion

In the present study we used the 12 lead electrocardiogram as a reference for the reproducibility of static postinfarction ST segment changes in 12 experimental leads. As might be expected no single lead reproduced all the changes in configuration shown by a full standard 12 lead electrocardiogram. We found that the reproducibility of regional ST segment changes increased, irrespective of the chosen lead, with increasing myocardial mass involved. The detection rate was highest in infarcts involving both the anterior and inferior left ventricular walls. It decreased as the extent of anterior free wall involvement decreased and was lowest in inferior infarcts. The importance of infarct extension is apparent in fig 2. For

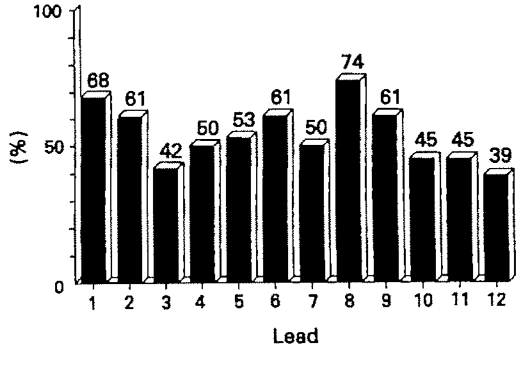


Figure 4 Detection rate (%) of ST segment deviation in 12 experimental leads. Leads are defined in table 1.

Table 2 Number of times ST segment deviation was recorded in three selected experimental leads alone or in combination

Main lead	Second lead 8	7	12
All infarcts: (n = 38)			
8	28	29	31*
7		19	22*
12			15
Small infarcts: (n = 21)			
8	12	13	15†
7		7	9†
12			6
Large infarcts: (n = 17)			
8	16	16	16‡
7		12	13‡
12			9

For definition of infarcts see text.
*p = 0·02; †p = 0·06, ‡NS.

large infarcts the detection rate was almost equal in the 12 study leads, whereas an increased disparity was seen as the infarct size decreased. These results accord with earlier studies. In patients with previous myocardial infarction Castellanet *et al* found a significantly lower detection rate for residual inferior ischaemia compared with residual anterior ischaemia.[2] Fox *et al* found that the number of leads reflecting myocardial ischaemia increased with the extent and severity of the ischaemia.[3]

Because oblique and sagittal leads "look" through the heart, and chest leads mainly scan the anterior aspects of the heart, oblique and sagittal leads might be better at detecting ischaemia in deeply located myocardial structures. These statements accord with the present study. We found that an oblique lead with one electrode in the V2 position (lead 8) had the highest detection rate, and was more successful than any other lead in patients with combined, extensive, apical, lateral, and inferior infarcts. In ambulatory monitoring CM5 (lead 7) is usually chosen for detection of anterior ischaemia. In the present study, however, many other leads were better than CM5 in patients with combined, extensive, and septal infarcts, and only in patients with apical or lateral infarcts did CM5 reliably detect ST segment deviations. Compared with other chest leads, only those with a more medially placed electrode were better than CM5. Chest leads had low detection rates in patients with inferior infarcts. The inferior lead (12) had a low detection rate in these patients too, detecting less than 50% of the ST segment changes: only sagittal and oblique leads with one electrode in the V2 position (leads 1 and 8) had a detection rate $\geq 50\%$ in patients with inferior infarcts.

For ambulatory monitoring two bipolar leads are usually available. Because the combination of CM5 and an inferior like lead is often used in ambulatory monitoring, we compared the 7, and 12 combination with all other possible combinations. In the total cohort with persistent ST segment deflections the detection rate of this 7 and 12 combination was exceeded by seven other combinations all of which included the inferior lead (12) and particularly by the combination of leads 8 and 12, which was significantly better. The main differences were found primarily in patients with small infarcts, in whom the 8 and 12 combination was better ($p = 0·06$) than the CM5 and inferior lead combination. Differences in detection rates for large infarcts between the different leads were small and little extra information was added when two leads were combined.

Our results would be taken to show that two lead ambulatory monitoring primarily detects extensive myocardial ischaemia and is less reliable in detecting ischaemia involving smaller segments. This statement accords with the results obtained in patients with dynamic ST segment changes. In patients recovering from acute myocardial infarction and in patients with stable coronary artery disease, exercise testing with a simultaneous 12 lead electrocardiogram detects significantly more ST segment deviations than does two lead ambulatory monitoring.[4-6] A positive ambulatory monitoring test, however, identified patients with more extensive electrocardiographic evidence of exercise induced ischaemia,[7] and was significantly correlated with mortality, reinfarction, and cardiac events.[8-10] Ambulatory ST segment deflections were primarily seen in patients who also had exercise induced ST segment changes,[7 11 12] and Holter monitoring did not add much information on the prevalence of ischaemia in patients with a sufficiently vigorous exercise test. In patients with exercise provoked ischaemia, however, ST segment deflections during ambulatory monitoring identified patients at an increased risk of subsequent cardiac events,[8 9] probably because they had extensive ischaemia. Before percutaneous transluminal coronary angioplasty in patients with single vessel coronary disease, ambulatory monitoring showed ST segment deviations in 63% of patients; 84% of the deviations were seen in CM5.[13] During percutaneous transluminal coronary angioplasty the detection rate was 100% whatever the site of the stenosis.

In four patients no significant ST segment deviations were found in the standard electrocardiogram. In one of them, two sagittal and two oblique leads showed significant deflections, but too few patients were studied for specificity to be calculated.

In ambulatory monitoring, extensive ischaemic electrocardiographic changes are better detected than smaller ones, and anterior changes better than inferior. No single lead or any combination of two leads fully displayed the information given by a standard electrocardiogram. CM5 primarily detected ischaemic changes in the lateral aspects of the left ventricle, whereas septal and inferior changes were partly missed. An oblique bipolar lead was significantly better than CM5, especially in small infarcts. When the oblique lead was combined with an inferior lead the overall detection rate increased and was significantly better than the combination of CM5 and the inferior lead.

1 Jespersen CM, Rasmussen V. Value of a bipolar modified inferior lead in detection of inferior mycardial ischaemia. *Br Heart J* 1988;60:287–9.

2 Castellanet MJ, Greenberg PS, Ellestad MH. Comparison of S-T segment changes on exercise testing with angiographic findings in patients with prior myocardial infarction. *Am J Cardiol* 1978;42:29–35.

3 Fox KM, Deanfield J, Ribero P, England D, Wright C. Projection of ST segment changes on to the front of the chest. Practical implications for exercise testing and ambulatory monitoring. *Br Heart J* 1982,48:555–9.

4 Gottlieb SO, Gottlieb SH, Achuff SC, *et al*. Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. *JAMA* 1988;259:1030–5

5 Bonaduce D, Petretta M, Lanzillo T, *et al*. Prevalence and prognostic significance of silent myocardial ischaemia detected by exercise test and continuous ECG monitoring after acute myocardial infarction. *Eur Heart J* 1991; 12:186–93.

6 Mulcahy D, Keegan J, Crean P, *et al*. Silent myocardial ischaemia in chronic stable angina. a study of its frequency and characteristics in 150 patients. *Br Heart J* 1988, 60:417–23.

7 Currie P, Saltissi S. Transient ischaemia after acute myocardial infarction: relationship to exercise ischaemia *Eur Heart J* 1991;12.395–400.

8 Rocco MB, Nabel EG, Campbell S, *et al*. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* 1988;78:877–84.

9 Deedwania PC, Carbajal EV Silent ischemia during daily life is an independent predictor of mortality in stable angina. *Circulation* 1990;81 748–56.

10 Ouyang P, Chandra NC, Gottlieb SO. Frequency and importance of silent myocardial ischemia identified with ambulatory electrocardiographic monitoring in the early in-hospital period after acute myocardial infarction. *Am J Cardiol* 1990;65:267–70.

11 Deedwania PC, Carbajal EV. Exercise test predictors of ambulatory silent ischemia during daily life in stable angina pectoris. *Am J Cardiol* 1990;66:1151–6.

12 Wilcox I, Freedman SB, Li J, Harris PJ, Kelly DT. Comparison of exercise stress testing with ambulatory electrocardiographic monitoring in the detection of myocardial ischemia after unstable angina pectoris. *Am J Cardiol* 1991;67:89–91.

13 Hoberg E, Schwarz F, Voggenreiter U, Kuebler W. Holter monitoring before, during and after percutaneous transluminal coronary angioplasty for evaluation of high-resolution trend recordings of lead CM$_5$ and CC$_5$ for ST-segment analysis. *Am J Cardiol* 1987;60:796–800.

There is now a monitoring system which incorporates the latest in advanced technology, and yet is still very easy to use.

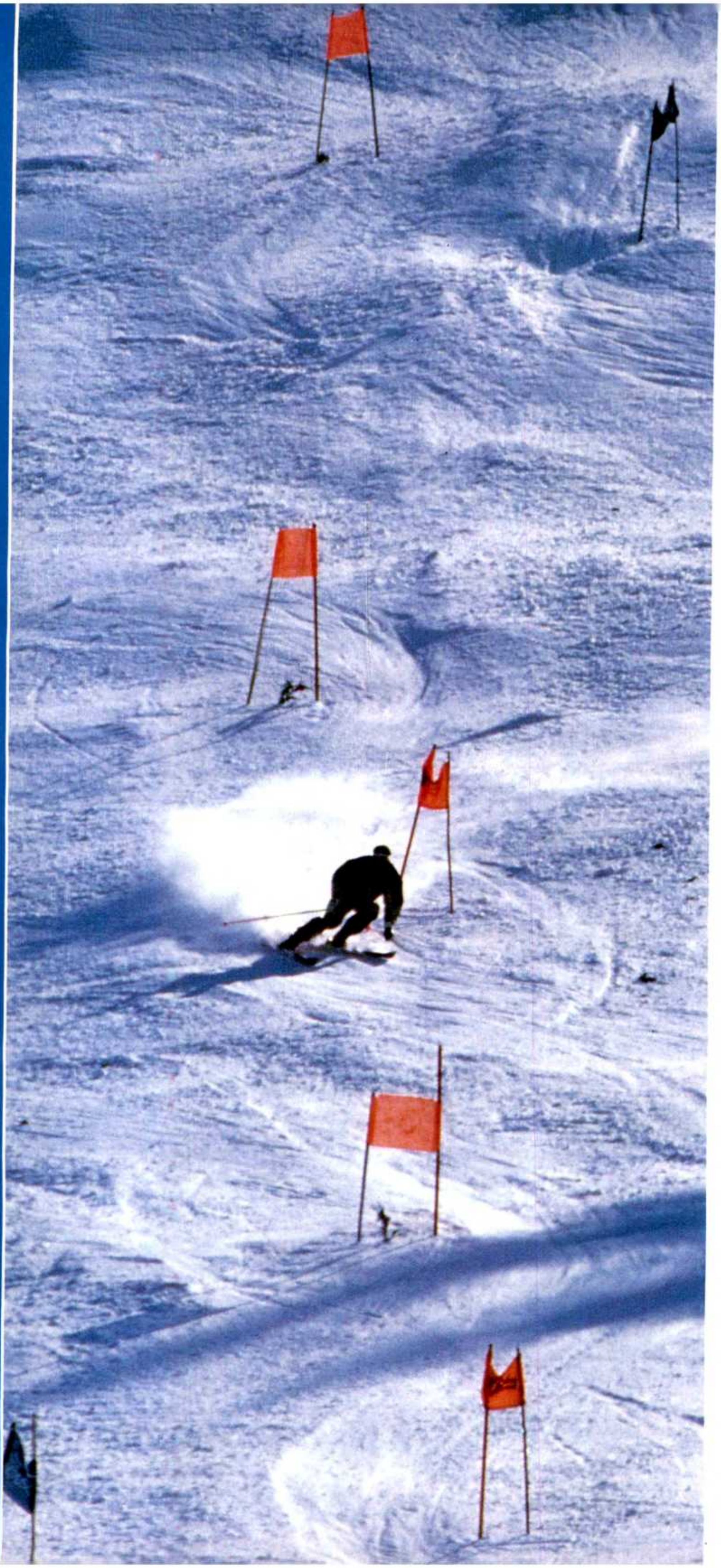
It features multiple microprocessors, open system architecture, parallel processing, custom designed chips, digital networking, surface mounted components, industry standard Ethernet compatibility, multilayered boards, 32 bit video chip, very high resolution programmable screen, infra-red remote control and instant communications with a multichannel colour central station.

The name of this system?

The *new* Athena NT

For further information contact Karen Demmon at S&W Vickers on 081-309 0433

SKIPPER PTCA CATHETER



Optimal trackability.

Negotiating a path through a tortuous anatomy isn't always easy.

You need a PTCA catheter that responds to the lightest of touches, allowing accurate tracking.

The new Skipper is such a touch-sensitive device. Your hand movements are precisely transmitted to the spring coil distal shaft, which is both pliant and flexible.

Designed and engineered in Europe, the Skipper doesn't fall down in any area.

You can push, track and cross with it, and the balloon is predictably compliant.

If you'd like full details, make tracks for your telephone and call Nycomed on 021-742 2444.

NYCOMED
INGENOR

Capoten treats hypertension whilst maintaining your patients quality of life.

Reducing breathlessness, fatigue and oedema[1], Capoten offers a new lease of life to your heart failure patients.

From early days for a bright future

Climbing stairs more easily, getting out and about, to the shops once again, or simply whiling away hours in the garden – life style is reassured by Capoten.

Capoten adds life to years in hypertension and heart failure – a response your patients will thank you for.

CAPOTEN™
CAPTOPRIL

Adds life to years
IN HYPERTENSION AND HEART FAILURE

Capoten Prescribing Information (abbreviated) CAPOTEN TABLETS **Presentation**: Tablets containing 12.5mg, 25mg or 50mg captopril. **Indication and Adult Dosage**: **Mild to moderate hypertension**: Capoten is indicated for first line treatment. The starting dose is 12.5mg bd. The usual maintenance dose is 25mg bd. This may be increased to 50mg bd. Treatment should be at the lowest effective dose. A thiazide diuretic may be added to Capoten if a satisfactory response has not been achieved. **Congestive heart failure**: Capoten is used together with diuretics, and where appropriate, digitalis, when diuretic therapy (such as frusemide 40-80mg or equivalent) is insufficient to control symptoms. Capoten must be started under close medical supervision. A starting dose of 6.25mg or 12.5mg may minimise any transient hypotensive effect. The usual maintenance dose is 25mg bd or tds. The usual maximum dose is 150mg daily. Delay dosage increases for at least 2 weeks, to determine if satisfactory response has occurred. A low initial dose is recommended in elderly patients who may have renal and other organ dysfunctions. **Contra-indications**: Hypersensitivity to captopril. Pregnancy and women of child bearing potential unless protected by adequate contraception. **Warnings/ Precautions**: Renal function should be assessed before and at appropriate intervals during therapy. Patients with renal impairment should not normally be treated with captopril. Do not use in patients with aortic stenosis or outflow tract obstruction. Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported but are rare in patients with normal renal function. Patients should report infections and Capoten withdrawn if neutropenia is suspected - See Data Sheet. Proteinuria is rare with prior normal renal function. Capoten should not be used routinely in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide. **Hypotension**: Symptomatic hypotension may occur occasionally with the firs one or two doses, usually relieved by the patient lying down. Aggressive diuretic therapy may exaggerate hypotensiv responses usually within one hour of the initial dose of Capoten. Significantly reducing or discontinuing the diuretic dose fo 4-7 days prior to initiating Capoten may reduce the possibility of this occurrence. First dose hypotension does not preclud subsequent dose titration. Hypotension has been occasionally reported in patients on Capoten due to causes of acute volum depletion such as vomiting or diarrhoea. Renal artery stenosis, surgery/ anaesthesia, lactation, clinical chemistry - see Dat Sheet. **Serum Potassium**: Potassium sparing diuretics or potassium supplements should not be used routinely as seru potassium is usually maintained in patients on diuretics with Capoten. **Side Effects**: See Warnings. Rashes, angioedema, tast disturbance and gastrointestinal upset, usually mild and transient, have been reported. **Overdosage**: see Data Sheet. **Dru Interactions**: see Data Sheet. **Product Licence Numbers:** Capoten Tablets 12.5mg PL 0034/0221; Capoten Tablets 25mg PL 0034/0193; Capoten Tablets 50mg PL 0034/0194. **Basic NHS Price**: 12.5mg tablets 100 - £18.86; 25mg tablets 90 - £19.34; 50mg tablets 90 - £32.95. **Legal category**: POM. Capoten is a Squibb Trade Mark. Further information available on request from: Technical Services Department, E.R. Squibb & Sons Limited, B.M.S. House, 141-149 Staines Road, Hounslow, Middx. TW3 3JA. Telephone 081 572 7422. Date of preparation: Dec '90. **Reference:** 1. Cannon PJ et al, J Am Coll Cardiol 1983; 2: 755-763.

SQUIBB®

Br Heart J 1992;68:291–5

Optimal control of myocardial ischaemia: the benefit of a fixed combination of atenolol and nifedipine in patients with chronic stable angina

Hassan El-Tamimi, Graham J Davies

Abstract

***Objective*—To study the effects on myocardial ischaemia of 50 mg of atenolol, 20 mg of slow release nifedipine, and their fixed combination given 12 hourly.**

***Design*—A treadmill exercise test and 24 hour ambulatory electrocardiographic monitoring were carried out after a period of five days off treatment (control) and at the end of three weeks of each treatment period.**

***Patients*—23 patients with stable angina pectoris, documented coronary artery disease, and a positive exercise test were randomised in a double blind, three way, cross over study.**

***Results*—Compared with the control, nifedipine significantly induced an increase in resting heart rate of (mean (SEM)) 14 (2) beats/min whereas atenolol and the combination significantly reduced it by 24 (2) and 20 (1) beats/min respectively. The number of exercise tests rendered negative after each intervention was five for nifedipine, nine for atenolol, and 11 for the combination. Compared with the control the time to the start of myocardial ischaemia (1 mm ST segment depression) during exercise significantly increased by 3·2 (0·6) min after nifedipine, by 4·6 (0·4) min after atenolol, and by 4·6 (0·5) min after the combination; rate-pressure product (beats/min. mm Hg) at 1 mm ST segment depression increased by 2824 (970) after nifedipine but fell by 4436 (900) and 4501 (719) after atenolol and the combination. The weekly frequency of angina was reduced from a mean of five while taking nifedipine, to three while taking atenolol, and to two while taking the combination. The total ischaemic time during ambulatory monitoring was significantly reduced from 69 (17) min during control to 37·5 (9·8) min during nifedipine, to 15·6 (5·5) min during atenolol, and to 6·5 (2·7) min during the combination.**

***Conclusion*—The undesirable effect of a high basal heart rate induced by nifedipine was neutralised by its combination with atenolol. Whereas atenolol and the combination were equally efficacious in controlling exercise induced ischaemia, the combination was more effective in reducing total ischaemic burden.**

(*Br Heart J* 1992;68:291–5)

In most patients with chronic stable angina, both an increase in myocardial oxygen consumption and a decrease in myocardial blood flow contribute to the development of ischaemia, whether symptoms occur at rest or during exercise.[1,2] β Blockers relieve ischaemia primarily by decreasing myocardial oxygen demand, and calcium channel blockers do so by improving myocardial oxygen supply. By acting on these different determinants of myocardial ischaemia, the combination of both drugs could provide better control of myocardial ischaemia.

We have investigated the anti-ischaemic effects of a calcium antagonist (nifedipine) and a β blocker (atenolol) singly and in a fixed combination on symptoms, and exercise induced and ambulatory ischaemia.

Patients and methods

Thirty patients were enrolled, but only 23 completed the study: 19 men and four women, aged 40 to 72 (mean 56·2) years, who had stable exertional angina of eight to 156 months duration (mean 56·2). The other seven patients were excluded at the end of the run in period because of a negative exercise test and were not included in the analysis. All patients had positive exercise tests for myocardial ischaemia (≥1 mm horizontal or downsloping ST segment depression, measured 60 ms after the J point) and documented coronary artery disease (five patients with one vessel, 11 patients with two vessel and seven patients with three vessel disease). There had been no change in the frequency, duration, or severity of their angina in the three months before the study. Four patients had suffered a previous Q wave myocardial infarction (≥ six months) before the study. All patients had normal blood pressure, were in sinus rhythm, and had no evidence of heart failure, cardiomyopathy, or valvar heart disease. No patient had evidence of left ventricular hypertrophy or conduction defects on the electrocardiogram, which could have interfered with the interpretation of ST segment changes, and no patient was taking digitalis.

Cardiovascular Research Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London
H El-Tamimi
G J Davies

Correspondence to:
Dr H El-Tamimi,
Division of Cardiology,
University of Florida College of Medicine, 1600 Archer Road, PO Box 100277,
Gainesville, Florida 32610-0277, USA.

Accepted for publication
20 September 1991

STUDY PROTOCOL

The protocol was approved by the Hammersmith Hospital research ethics committee and all patients gave fully informed written consent for the study. All patients had already undergone at least two diagnostic treadmill exercise tests. Anti-anginal treatment was discontinued for five days before the study, but patients were free to use sublingual glyceryl trinitrate as required; no exercise test was performed within four hours of the last sublingual treatment with this drug. After a two week single blind run in period with 50 mg of atenolol twice daily, a randomised, double blind, three way cross over study was performed in which 50 mg of atenolol, 20 mg of slow release nifedipine, and their fixed combination were given twice daily for three weeks.

Treadmill exercise testing and 24 hour ambulatory electrocardiographic monitoring were used to detect myocardial ischaemia on day 5 while off treatment and at the end of each treatment period. Patients kept angina diaries throughout the trial period, and were asked to record the number of anginal attacks and their use of glyceryl trinitrate.

EXERCISE TESTING

Exercise testing was performed with the modified Bruce protocol on a computerised treadmill system (Marquette case 12). Twelve lead electrocardiogram recording and blood pressure measurement (cuff) were taken at rest, at the end of each minute during exercise, at the point of 1 mm (0·1 mV) ST segment depression, at peak exercise, and three and six minutes into the recovery period. Three electrocardiogram leads were monitored continuously before and during exercise and for six minutes into recovery. All tests were performed at the same time of day, four to six hours after the last dose of treatment for each patient. A positive exercise test diagnostic of myocardial ischaemia was defined as horizontal or downsloping ST segment depression ≥1 mm measured 60 ms after the J point with respect to the resting value. The exercise test was stopped in the event of chest pain of moderate severity, ST segment depression ≥2 mm, or inability of the patient to exercise further.

For all exercise tests, exercise duration (minutes) was measured and heart rate-systolic blood pressure product (beats/min. mm Hg) calculated at 1 mm ST segment depression or, when the exercise test was negative at peak exercise, and the value of the rate-pressure product was used as an index of the ischaemic threshold. The reason for stopping the test was noted.

AMBULATORY HOLTER MONITORING

Ambulatory electrocardiographic recordings were taken from prejelled electrodes, positioned after careful skin preparation to record 2 bipolar leads (modified lead III and an anterior lead), with 2 channel amplitude modulated recorders (Marquette 8500). The anterior lead selected for each patient was that which had no Q wave and had shown maximal ST segment depression during exercise. All patients were instructed to continue their normal daily activity and to use glyceryl trinitrate only for symptomatic relief. An episode of myocardial ischaemia was defined as horizontal or downsloping ST segment depression or ST segment elevation ≥1 mm (0·1 mV) at 60 ms from the J point, of more than one minute duration and separated from the next episode by at least two minutes of baseline electrocardiogram.

DATA ANALYSIS

For each exercise test the level of the ST segment, 60 ms after the J point, was calculated after signal averaging by a computer assisted system in all 12 leads every minute with an accuracy of 0·1 mm. The lead showing the greatest ST segment depression was selected for analysis. The values then measured were: exercise time (minutes) and heart rate-blood pressure product (beats/min. mm Hg) at the start of 1 mm ST segment depression; if the exercise test was negative, the values were taken at peak exercise. The reason for stopping the test was noted. The exercise tests were analysed by people blinded to the treatment.

The tapes taken during ambulatory electrocardiographic monitoring were analysed (blind as to treatment) with a Marquette Laser Holter System 800. The total duration of myocardial ischaemia was measured from each 24 hour period.

STATISTICAL ANALYSIS

The statistical analysis was performed by analysis of variance with pairs compared by *t* test. A p value <0·05 was considered statistically significant. Data are expressed as mean (SEM).

Results

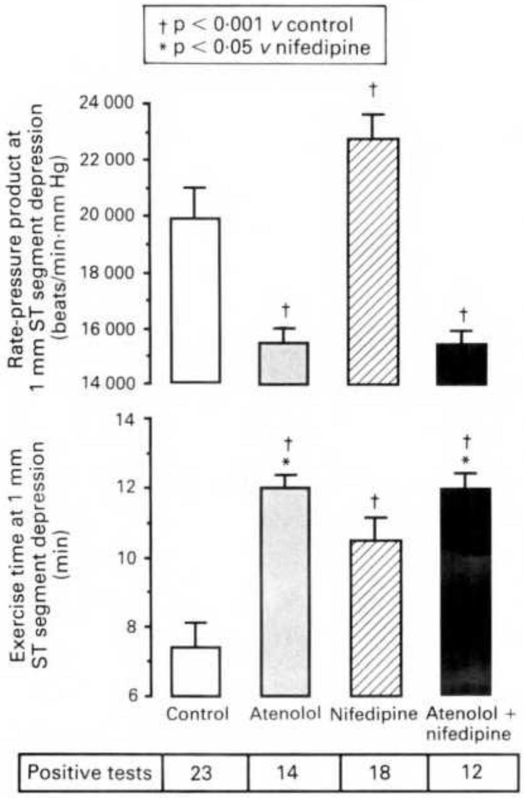
CONTROLS

The exercise tests in all patients were positive for myocardial ischaemia while they were not taking drugs (control). The exercise test was stopped because of severe chest pain in 14 patients and silent ST segment depression ≥2 mm in nine patients. The exercise time and rate-pressure product at 1 mm ST segment depression were 7·4 (0·8) min and 20 041 (1046) beats/min. mm Hg respectively (fig 1). The total ischaemic time during ambulatory monitoring was 69 (17·1) min (fig 2).

EFFECT OF NIFEDIPINE

At the end of the period of taking nifedipine, in five patients the exercise test was negative and was stopped due to fatigue. Of 18 patients who had positive test 12 stopped due to chest pain and one due to shortness of breath; the remaining five were stopped due to silent ST segment depression >2 mm. Compared with the control, the exercise time to 1 mm ST segment depression increased from 7·4 (0·8) to 10·6 (0·7) min (p < 0·001). This increment was also associated with an increase in the rate-pressure product at 1 mm ST segment depression from

Figure 1 Bar graph of changes in rate-pressure product and exercise time at 1 mm ST segment depression and number of positive exercise tests for control periods, treatment with atenolol, nifedipine, and the combination of atenolol and nifedipine (mean (SEM)). Atenolol and the combination significantly reduced rate-pressure product and increased exercise time with fewer positive tests compared with nifedipine alone.



Positive tests	23	14	18	12

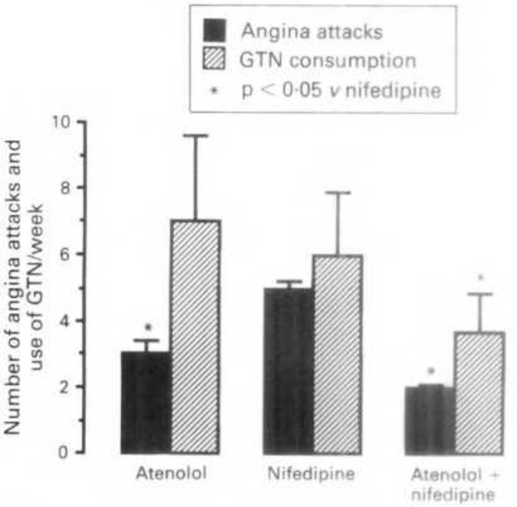


Figure 3 Bar graph showing number of anginal attacks and use of glyceryl trinitrate (GTN) consumption (mean (SEM)). Combination of atenolol and nifedipine significantly reduced anginal attacks and use of glyceryl trinitrate compared with nifedipine alone.

20 041 (1046) to 22 865 (841) ($p < 0·001$) (fig 1). The total ischaemic time during ambulatory monitoring was reduced from 69 (17·1) to 37·5 (9·8) min ($p < 0·01$) (fig 2). The average number of anginal attacks during this period was 5 (0·2) and the use of glyceryl trinitrate was 6 (1·9) per week (fig 3).

EFFECT OF ATENOLOL

At the end of the period of taking atenolol nine patients had a negative exercise test and stopped due to fatigue. Of 14 patients who had positive tests, five were stopped because of chest pain, three due to shortness of breath and the remaining six due to silent ST depression >2 mm. Atenolol increased exercise time to 1 mm ST segment depression from 7·4 (0·8) to 11·9 (0·4) min ($p < 0·001$ *v* control; $p < 0·05$ *v* nifedipine). This was associated with a reduction in the rate-pressure product at 1 mm ST segment depression from 20 041 (1046) to 15 605 (499) ($p < 0·01$ *v* control and nifedipine) (fig 1). The total ischaemic time during ambulatory monitoring was reduced further from 69 (17·1) to 15·6 (5·5) min ($p < 0·01$ *v* control; $p < 0·005$ *v* nifedipine) (fig 2). The average number of anginal attacks a week during this period was 3 (0·4) ($p < 0·05$ *v* nifedipine) and the use of glyceryl trinitrate was 7 (2·6) per week (fig 3).

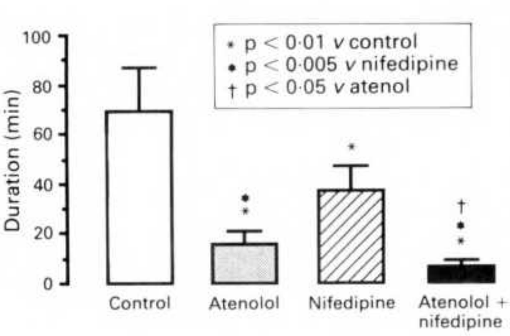
EFFECT OF THE FIXED COMBINATION OF ATENOLOL AND NIFEDIPINE

At the end of the period of taking the combination of atenolol and nifedipine, 11 patients had a negative exercise test and it was stopped due to fatigue. Twelve patients had positive tests; three stopped due to chest pain, four due to shortness of breath and five due to silent ST segment depression >2 mm. Exercise time to 1 mm ST segment depression increased from 7·4 (0·8) to 11·9 (0·4) min ($p < 0·0001$ *v* control; $p < 0·05$ *v* nifedipine); this was associated with a reduction in the rate-pressure product at 1 mm ST segment depression from 20 041 (1046) to 15 540 (488) ($p < 0·001$ *v* control, and nifedipine) (fig 1). The total ischaemic time during ambulatory monitoring was reduced from 69 (17·1) to 6·5 (2·7) min ($p < 0·01$ *v* control and nifedipine; $p < 0·05$ *v* atenolol) (fig 2). The average number of anginal attacks during this period was reduced to 2 (0·1) ($p < 0·05$ *v* nifedipine) and the use of glyceryl trinitrate to 3·7 (1·2) times a week ($p < 0·05$ *v* nifedipine, fig 3).

EFFECT OF ATENOLOL, NIFEDIPINE, AND THEIR COMBINATION ON HEART RATE

Compared with the control the resting heart rate was increased by 13 (7) beats/min with nifedipine ($p < 0·001$) but was reduced by 22 (7) beats/min by atenolol and 19 (7) by the combination ($p < 0·001$). Figure 4 gives the heart rate measured minute by minute during the exercise tests, and shows that nifedipine resulted in a higher heart rate throughout exercise when compared with control, atenolol, and the combination of atenolol and nifedipine.

Figure 2 Bar graph showing mean total duration of ischaemia on ambulatory electrocardiographic monitoring for control periods and during treatment with atenolol, nifedipine, and combination of atenolol and nifedipine (mean (SEM)). The combination significantly reduced total ischaemic time compared with all other groups.



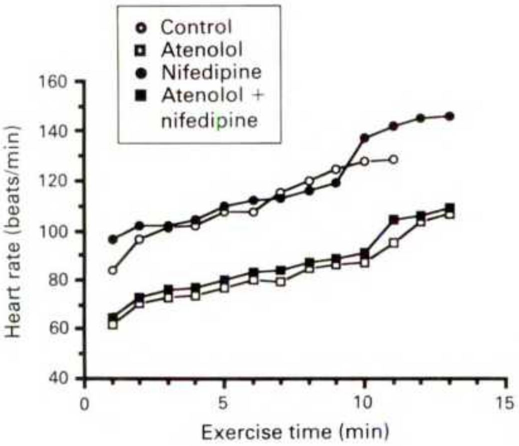


Figure 4 Mean heart rate during the exercise test for control periods and during treatment with atenolol, nifedipine, and combination of atenolol and nifedipine. Nifedipine induced a significant reflex increase in resting heart rate compared with the other groups. For each level of exercise, heart rate was significantly lower with atenolol than with nifedipine, and similar to that with atenolol and nifedipine combined.

Discussion

Many of the patients with chronic stable angina often show an unpredictable variability of effort tolerance and even have occasional spontaneous attacks of angina at rest.[3] In these patients ischaemia can be caused by an increase in myocardial oxygen demand that increases with a rise in the heart rate, contractility, or intraventricular volume and pressure. Alternatively, it can be caused by a reduction in myocardial blood flow due to dynamic constriction at the site of a stenosis of an epicardial coronary artery,[4] by an increase in coronary arteriolar resistance,[5] or by an increase in left ventricular wall tension that reduces subendocardial blood flow.[6] The options for treatment in these patients lie in choosing a drug that acts on all these different factors of myocardial ischaemia. Because one anti-anginal drug usually modifies only a few of these, the addition of a second agent with different pharmacological actions may act in a complementary fashion to control myocardial ischaemia.

This study shows that a fixed combination of atenolol and nifedipine is more effective than either drug alone in reducing ischaemia detected by Holter monitoring during unrestricted daily life. It is also more effective than nifedipine alone in reducing the number of anginal attacks and the use of glyceryl trinitrate. The effects of the combination on exercise induced ischaemia assessed by standardised exercise testing was evident through a significant reduction of the ischaemic threshold compared with control and nifedipine alone, and was similar to that found with atenolol alone. It has also been shown that the combination increases the left ventricular ejection fraction with almost complete abolition of angina pectoris when compared with either drug alone.[7]

In our study nifedipine induced an increase in exercise time to 1 mm ST segment depression but resulted in a negative exercise test in only five out of the 23 patients. It also had a modest but significant effect on ambulatory ischaemia. It has been shown that nifedipine relieves ischaemia primarily by improving myocardial perfusion by antagonising vasoconstriction at the site of a stentic lesion[8] or by improving collateral blood flow to ischaemic regions.[9] The systemic vasodilatory effect of nifedipine also acts to reduce myocardial consumption of oxygen but the peripheral action stimulates reflex action of the sympathetic nervous system.[10] The resulting increases in heart rate may reduce the antianginal effects of this drug[11] and account for our finding of only a small beneficial effect.

In our study, atenolol alone significantly increased the exercise time to 1 mm ST segment depression compared with nifedipine alone and made nine out of 23 exercise tests negative. This was achieved by a reduction of the heart rate at rest and during exercise (patients reached a mean maximum heart rate of only 100 beats/min after exercising for nearly 15 minutes) (fig 4). Atenolol also reduced the total duration of ambulatory ischaemia, further than nifedipine, by 77% of the control value. It also had a beneficial effect on the number of anginal attacks when compared with nifedipine monotherapy. β Blockers are known to relieve ischaemia primarily by decreasing myocardial oxygen demand through inhibition of the rise in heart rate and blood pressure that accompanies submaximal and maximal exercise.[12] They have been shown in other studies to be effective in reducing ischaemia during ambulatory activities.[13] The fixed combination of atenolol and nifedipine produced effects during exercise testing similar to those found with atenolol alone, and also produced similar behaviour of the heart rate (fig 4).

In conclusion atenolol and its combination with sustained release nifedipine are equally efficacious in controlling that aspect of stable angina which is due to dynamic exercise alone. This effect is explained by the similar behaviour of heart rate during exercise with both preparations. The additional benefit, however, of the combination on ambulatory ischaemia during unrestricted daily life is consistent with the effect of nifedipine on that component of chronic angina determined by variations in vasomotor tone. The potentially adverse effect of the high resting heart rate induced by nifedipine on the dynamic exercise component of angina is neutralised by its combination with atenolol.

1 Maseri A. The changing face of angina pectoris. *Lancet* 1983;**1**:746–9.
2 Epstein SE, Talbot TL. Dynamic coronary tone in precipitation, exacerbation and relief of angina pectoris. *Am J Cardiol* 1981;**48**:797–803.
3 Maseri A. Medical therapy of chronic stable angina pectoris. *Circulation* 1990;**82**:2258–62.
4 Gage JE, Hess OM, Murakami T, Ritter M, Grimm J, Krayenbuehli HP. Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. *Circulation* 1986;**73**:865–75.
5 Cannon RO III, Watson RM, Rosing DR, Epestine SE. Angina caused by reduced vasodilator reserve of the small coronary arteries. *J Am Coll Cardiol* 1983;**1**:1359–73.
6 Ellis AK, Klocke FJ. Effect of preload of the transmural distribution of perfusion and pressure flow relationship in the canine coronary vascular bed. *Circ Res* 1980;**46**:68–77.
7 Findlay IM, MacLeod K, Ford M, Gillen G, Elliott A, Dargie HJ. Treatment of angina pectoris with nifedipine and atenolol: efficacy and effect on cardiac function. *Br Heart J* 1986;**55**:240–5.
8 Gunther S, Green L, Mulbr JE, Mudge GH Jr, Grossman W. Prevention by nifedipine of abnormal coronary vasoconstriction in patients with coronary artery disease. *Circulation* 1981;**63**:849–55.

9 Rache RJ, Tockman BA. Effect of nitroglycerin and nifedipine on subendocardial perfusion in the presence of a flow-limiting coronary stenosis in the awake dog *Circ Res* 1982;50:678–87.

10 Lown B. Introduction. Symposium on nifedipine and calcium flux inhibitors in the treatment of coronary artery spasm and myocardial ischaemia *Am J Cardiol* 1979, 44:780–2.

11 Schanzenbacher P, Liebau G, Deeg P, Kochsiek K. Effect of intravenous and intracoronary nifedipine on coronary blood flow and myocardial oxygen consumption *Am J Cardiol* 1983,51·712–7.

12 Subramanian VB, Bowles MU, Davies AB, Raftery EB. Calcium channel blockade as primary therapy for stable angina pectoris: a double-blind placebo-controlled comparison of verapamil and propranolol. *Am J Cardiol* 1982,50:1158–63

13 Dargie HJ, Lynch PG, Krikler DM, Harris L, Krikler S Nifedipine and propranolol. a beneficial drug interaction. *Am J Cardiol* 1981,71:676–82.

Br Heart J 1992;68:296–300

Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing "athlete's heart" from hypertrophic cardiomyopathy

Jannet F Lewis, Paolo Spirito, Antonio Pelliccia, Barry J Maron

National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA
P Spirito
B J Maron

Division of Cardiology, Department of Medicine, Howard University College of Medicine, Washington, DC, USA
J F Lewis

Institute of Sports Science, Department of Medicine, Italian National Olympic Committee, Rome, Italy
A Pelliccia

Correspondence to
Dr Jannet F Lewis, National Institutes of Health, Building 10, Room 7B-15, Bethesda, Maryland 20892, USA.

Accepted for publication
19 February 1992

Abstract

***Objective*—In some athletes with a substantial increase in left ventricular wall thickness, it may be difficult to distinguish with certainty physiological hypertrophy due to athletic training from hypertrophic cardiomyopathy. The purpose of the present investigation was to determine whether assessment of left ventricular filling could differentiate between these two conditions.**

***Design*—Doppler echocardiography was used to obtain transmitral flow velocity waveforms from which indices of left ventricular diastolic filling were measured. Normal values were from 35 previously studied control subjects.**

***Setting*—Athletes were selected mostly from the Institute of Sports Science (Rome, Italy), and patients with hypertrophic cardiomyopathy were studied at the National Institutes of Health (Bethesda, Maryland).**

***Participants*—The athlete group comprised 16 young competitive athletes with an increase in left ventricular wall thickness (range 13–16 mm; mean 14). For comparison, 12 symptom free patients with non-obstructive hypertrophic cardiomyopathy were selected because their ages and degree of hypertrophy were similar to those of the athletes.**

***Results*—In the athlete group, values for deceleration of flow velocity in early diastole, peak early and late diastolic flow velocities, and their ratio were not significantly different from those obtained in untrained normal subjects; furthermore, Doppler diastolic indices were normal in each of the 16 athletes. Conversely, in patients with hypertrophic cardiomyopathy, mean values for Doppler diastolic indices were significantly different from both normal subjects and athletics (p = 0·01 to 0·003), and one or more indices were abnormal in 10 (83%) of the 12 patients.**

***Conclusions*—Doppler echocardiographic indices of left ventricular filling may aid in distinguishing between pronounced physiological hypertrophy due to athletic training and pathological hypertrophy associated with hypertrophic cardiomyopathy.**

(*Br Heart J* 1992;68:296–300)

Athletic training is often associated with a modest increase in left ventricular cavity size during diastole, ventral wall, wall thickness, and mass.[1–10] Some athletes, however, may show considerable increase in left ventricular wall thickness.[9] In such athletes, the presence of primary pathological hypertrophy due to hypertrophic cardiomyopathy may be difficult to exclude on a morphological basis alone.[11 12]

Pulsed Doppler echocardiography has been used extensively to assess left ventricular diastolic filling in normal subjects and in patients with various cardiac diseases[13–20] including hypertrophic cardiomyopathy. Although previous studies have shown normal diastolic filling patterns in athletes with normal or mild left ventricular wall thickening,[21–25] Doppler echocardiography has not been used to clarify the differential diagnosis between pronounced physiological hypertrophy due to athletic training ("athlete's heart") and hypertrophic cardiomyopathy. The present investigation applies Doppler indices of left ventricular diastolic filling to this clinical problem.

Methods

STUDY POPULATIONS

Our study population comprised 16 highly trained competitive athletes selected because of a considerable increase in left ventricular wall thickness ($\geqslant 13$ mm). Fourteen were selected from a large group of elite Italian athletes who were all members of national teams and were evaluated at the Institute of Sports Science (Rome, Italy) between 1986 and 1988, as part of a mandatory annual medical evaluation.[9] The other two athletes were selected from a group of competitive collegiate athletes at the University of Maryland, 1984–5.[26] These 16 athletes participated in rowing (11), canoeing (two), cycling (one), football (one), and running (one). Ages ranged from 18 to 26 (mean 22); all were men. Each athlete had normal blood pressure at the time of the evaluation, and none had a history of systemic hypertension or a family history of sudden cardiac death or hypertrophic cardiomyopathy.

Twelve patients with hypertrophic cardiomyopathy were also included. These patients were selected so that they would closely resemble the athletes in the study, by meeting the criteria: (*a*) comparatively mild left ventricular hypertrophy (for patients with hypertrophic cardiomyopathy)[7 9] with maximum wall thickness ⩽18 mm; (*b*) ⩽30 years of age; (*c*) symptom free; (*d*) absence of systolic anterior motion of the mitral valve and haemodynamically significant mitral regurgitation; and (*e*) no history of athletic training. Patients ranged in age from 11 to 30 (mean 23) years, and three were younger than 18 (11, 16, and 17); 10 (83%) were men. Genetic transmission of hypertrophic cardiomyopathy was documented by clinical or echocardiographic findings in one or more relatives of nine of the 12 patients[27]; the relatives of the other three patients did not undergo systematic echocardiographic studies. No patient was taking cardioactive drugs at the time of the study. Systemic blood pressure was within normal limits in each patient with hypertrophic cardiomyopathy.

Doppler echocardiographic findings in athletes and patients with hypertrophic cardiomyopathy were compared with values taken in our laboratory from 35 untrained normal subjects (mean age 22, range 19 to 29 years) without cardiovascular disease.[15]

ECHOCARDIOGRAPHY

Echocardiographic studies were carried out with an Advanced Technology Laboratory Mark 500 mechanical sector scanner or a Hewlett Packard 77020AC phased array sector scanner with a 2·5 or 3·5 mHz transducer. Images were obtained in multiple cross sectional planes by standard transducer positions.[28] Magnitude and distribution of left ventricular hypertrophy were assessed from the cross sectional echocardiogram by previously described methods.[11]

M mode echocardiograms were derived from the cross sectional images under direct anatomical view and recorded on a strip chart at 50 mm/s paper speed. Measurements of cardiac dimensions were taken from the M mode echocardiogram according to the recommendations of the American Society of Echocardiography.[29]

DOPPLER ECHOCARDIOGRAPHY

Each subject was examined in the left lateral decubitus position by Doppler echocardiography with the transducer at or slightly to the left of the apical impulse. The transducer was orientated to get an apical four chamber view of the heart that provided a good visualisation of the left ventricular cavity and maximal movement of the mitral valve leaflets. The Doppler cursor line was then positioned through a plane orientated perpendicularly to the mitral annulus and crossing the left ventricle from apex to centre of the anulus. Care was taken to minimise the angle between the presumed direction of diastolic transmitral blood flow and the ultrasound beam (cursor); this angle was estimated to be less than 20 degrees in each subject. The Doppler sample volume was positioned in the inflow area of the left ventricle between the mitral leaflets to maximise the peaks of diastolic flow velocity with the best graphic quality of the waveforms; the highest diastolic velocities were usually identified within the left ventricular cavity about 1 cm below the mitral anulus.

Table 1 Diastolic Doppler indices of left ventricular filling in competitive athletes with left ventricular hypertrophy, patients with non-obstructive hypertrophic cardiomyopathy (HCM), and untrained normal subjects (mean (SD))

	Untrained normal controls		*Athletes*		*HCM*	
No of subjects	35		16		12	
Age (y)	22	(2)	22	(3)	23	(6)
RR interval (ms)	1078	(148)	208	(158)†	1038	(174)
EF slope (cm/s²)	55	(12)	51	(8)*	39	(18)‡
Peak E (cm/s)	69	(11)	69	(11)*	59	(14)‡
Peak A (cm/s)	27	(6)	30	(9)	37	(13)‡
E A ratio	2 7	(0 8)	2 4	(0 6)*	1 7	(0 6)‡

*p = 0 04–0 005, athletes *v* HCM, †p = 0 01, athletes *v* HCM and controls; ‡p = 0 01 to 0 0003, HCM *v* controls.

EF slope, rate of deceleration of flow velocity in early diastole, Peak E, peak flow velocity in early diastole; Peak A, peak flow velocity in late diastole, E:A ratio, ratio of early to late peak flow velocity

Doppler waveforms were recorded on a strip chart at 100 mm/s paper speed. In each subject, three cardiac cycles with the most clearly defined flow velocity waveforms and the highest early diastolic peaks of flow velocity were selected for analysis.[15] Left ventricular diastolic flow velocity waveforms from three cardiac cycles were measured and values averaged for the Doppler diastolic indices: (*a*) early diastolic peak flow velocity, measured as the height of the early peak of flow velocity (E); (*b*) rate of decrease (deceleration) of flow velocity in early diastole (EF slope); (*c*) late diastolic peak flow velocity, measured as the height of the late (atrial) peak of flow velocity (A); and (*d*) the ratio of the early to late peaks of flow velocity (E/A). These Doppler diastolic indices have already been shown to have satisfactory reproducibility.[30]

STATISTICAL ANALYSIS

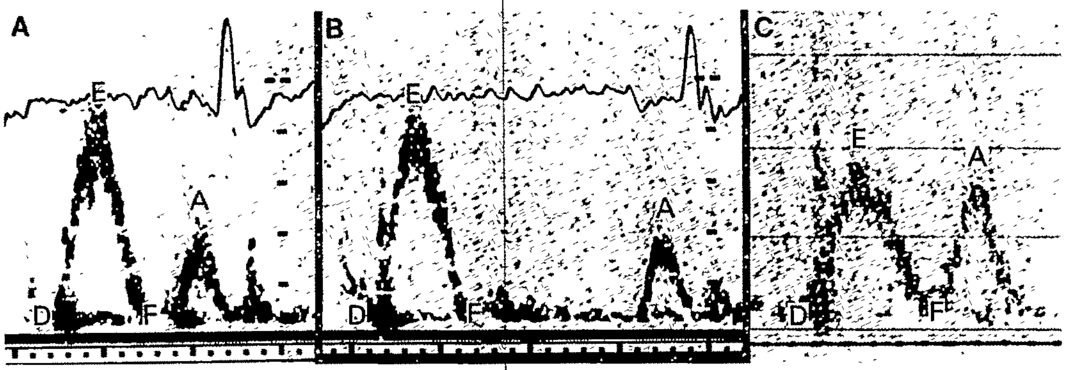
Data are expressed as mean (SD). Differences in Doppler indices of diastolic filling among athletes, patients with hypertrophic cardiomyopathy, and normal controls were assessed by analysis of variance. Comparisons between two groups of subjects were tested with the unpaired Student's *t* test. In individual subjects, any given Doppler diastolic index was considered abnormal when not within the 95% confidence intervals (95% CIs) of normal values.[15] Upper and lower normal 95% CIs for the Doppler diastolic indices had been calculated from the one tail of the Student's *t* test distribution as mean + (1 684 × SD), and mean − (1·684 × SD).[31] The transmitral waveform in each patient with hypertrophic cardiomyopathy (or athlete) was considered abnormal if the value for one or more of the Doppler indices of diastolic filling was outside this 95% CI.

Results

DOPPLER DIASTOLIC INDICES

Comparison of athletes and normal controls

In the athletes, mean values for deceleration of early diastolic flow velocity, early and late diastolic peak flow velocities, and the ratio of early to late peaks were similar and did not differ significantly from those of untrained, normal



(A) Waveforms of transmitral flow velocity taken with Doppler echocardiography in a sedentary 20 year old man without cardiovascular disease; (B) an 18 year old highly trained football player; (C) a sedentary 19 year old symptom free patient with hypertrophic cardiomyopathy and relatively mild left ventricular hypertrophy. (A) Normal diastolic waveform; deceleration of flow velocity in early diastole (EF slope) is rapid, and the height of early diastolic peak of flow velocity (E) is more than twice that of late diastolic peak A. (B) Pattern of the transmitral flow velocity waveform is similar to that of subject shown in panel (A). (C) Abnormal pattern of transmitral flow velocity; deceleration of flow velocity in early diastole (EF slope) is decreased and the ratio of peak early (E) to peak late flow velocity (A) is reduced. Each vertical division represents a 20 cm/s increment in flow velocity. Horizontal time line divisions are 40 ms apart.

subjects (table 1). Also, individual subject analysis showed that each index of diastolic filling of the left ventricle was within the 95% CI of the normal subjects in 15 of the 16 athletes (fig). The remaining athlete had only a mild increase in both the early and late peak flow velocities that were considered to occur as a normal consequence of increased stroke volume in this particular subject. Thus all 16 athletes had normal transmitral flow velocity waveforms. Heart rate in athletes was slower compared with normal controls (RR interval 1208 (158) *v* 1078 (148) ms, $p < 0\cdot1$).

Comparison of patients with hypertrophic cardiomyopathy and normal controls

In patients with hypertrophic cardiomyopathy, mean values for each of the Doppler diastolic indices measured were significantly different from those in the untrained normal subjects—that is, patients with hypertrophic cardiomyopathy showed decreased early peak flow velocity, slowed deceleration of early diastolic flow velocity, and increased late peak flow velocity associated with atrial systole. Heart rates in the two groups were not significantly different (table 1). Furthermore, individual patient analysis showed that indices of left ventricular filling exceeded the 95% CI of the untrained normal subjects in 10 (83%) of the 12 patients with hypertrophic cardiomyopathy (fig). Of these 10 patients, three had one abnormal index, six had two abnormal indices, and one had three abnormal indices. The abnormalities of diastolic filling that occurred in patients with hypertrophic cardiomyopathy included decrease in early diastolic peak flow velocity (<49 cm/s) in five patients, reduced deceleration of early diastolic flow velocity (<35 cm/s) in five patients, increased late diastolic peak flow velocity (<39 cm/s) in four patients, and reduced ratio of early to late peak flow velocities (<1·7) in four patients.

Comparison of athletes and patients with hypertrophic cardiomyopathy

In athletes mean values for deceleration of early diastolic flow velocity, early peak flow velocity, and the ratio of early to late peak velocities were significantly different from those from patients with hypertrophic cardiomyopathy ($p < 0\cdot05$), (table 1). Late diastolic peak flow velocity was similar in athletes and patients (table 1).

CARDIAC DIMENSIONS

Athletes

In the 16 athletes, thickness of the ventricular septum ranged from 13 to 16 (mean 14) mm and thickness of the posterior free wall ranged from 10 to 13 (mean 12) mm. Substantial hypertrophy was confined to the ventricular septum in 13 athletes, and involved both septum and contiguous anterior free wall in three. The cavity dimension of the ventricle at end diastole ranged from 47 to 63 (mean 58) mm and was >55 mm in 13 of the 16 athletes.

Hypertrophic cardiomyopathy

In the 12 patients with hypertrophic car-

Table 2 Cardiac dimensions in competitive athletes with left ventricular hypertrophy and patients with hypertrophic cardiomyopathy (HCM)

	Athletes (n = 16)		*HCM (n = 12)*		
	Mean (SD)	*Range*	*Mean (SD)*	*Range*	*p Value*
Age (y)	22 (3)	18–26	23 (6)	11–30	NS
Ventricular septal thickness (mm)	14 (1)	13–16	15 (2)	13–18	NS
Left ventricular posterior wall thickness (mm)	12 (1)	10–13	11 (1)	7–13	<0·05
Left ventricular end diastolic cavity dimension (mm)	58 (5)	47–63	45 (5)	38–56	<0·001

diomyopathy, thickness of the ventricular septum ranged from 13 to 18 (mean 15) mm, and did not differ from that in the athletes (table 2). Thickness of the posterior free wall ranged from 7 to 13 (mean 11) mm and was slightly smaller than that in the athletes ($p < 0.05$) (table 2). Left ventricular hypertrophy was confined to the anterior ventricular septum in eight patients and involved both the septum and portions of the contiguous anterior free wall in the remaining four. The cavity dimension of the left ventricle at end diastole ranged from 38 to 56 mm and the mean value was significantly smaller than that in the athletes (45 (5) *v* 58 (5) mm, $p < 0.001$).

Discussion

Long-term athletic training is known to produce physiological alterations in cardiac morphology that have been commonly referred to as the "athlete's heart".[7 10] These changes usually consist of a modest increase in either cavity size of the left ventricle at diastole, ventricular wall thickness, or both.[1–10] A minority of highly trained athletes, however, may show more substantial increases in thickness of the left ventricular wall (up to 16 mm).[9] On the other hand, hypertrophic cardiomyopathy is also characterised by increased thickness of the left ventricular wall. Whereas most patients with hypertrophic cardiomyopathy show a pronounced increase in left ventricular wall thickness of 20 mm or more, some patients with this disease may have mild increases in wall thickness of only 13–15 mm.[12 27 32] Hence, individual athletes with substantial left ventricular wall thickening create a diagnostic dilemma as it may be difficult to distinguish the "athlete's heart" from hypertrophic cardiomyopathy with comparatively mild left ventricular hypertrophy. The importance of this differential diagnosis becomes evident when one considers that the "athlete's heart" is a physiological condition not known to be associated with adverse pathological consequences, whereas hypertrophic cardiomyopathy seems to be the most common cause of sudden death in young competitive athletes.[32–34]

Several approaches have been suggested for the differential diagnosis between pronounced physiological hypertrophy and hypertrophic cardiomyopathy in athletes. Firstly, if hypertrophic cardiomyopathy can be documented in a relative of the athlete, this finding is strong evidence for genetically transmitted hypertrophic cardiomyopathy; however, about 45% of patients with hypertrophic cardiomyopathy have no evidence of familial transmission of the disease, and consequently a negative family study in the athlete does not absolutely exclude the possibility of hypertrophic cardiomyopathy.[27] Secondly, as physiological left ventricular hypertrophy may show regression within weeks after the end of training,[7 35] a period of planned deconditioning may induce a decrease in wall thickness in selected athletes that in turn would support the presence of physiological hypertrophy.[7] The small changes in thickness of the wall of the left ventricle, however, that are induced by deconditioning may be difficult to identify reliably by echocardiography in the individual subject. Thirdly, the assessment of absolute size of the left ventricular cavity at end diastole may be useful in this differential diagnosis; for example, a small cavity (< 45 mm) would strongly suggest hypertrophic cardiomyopathy, whereas a cavity > 55 mm would favour the training effect of the "athlete's heart".[7 10] In our study, the cavity dimension of the left ventricle at end diastole was in fact greater in athletes compared with patients with hypertrophic cardiomyopathy, although there was some overlap between the two groups. It should be emphasised, however, that the athletes in the study were mostly world class elite competitors who were engaged in particularly vigorous training programmes combining isotonic (endurance) and isometric (power) exercise. As a consequence, such subjects could be expected to have a larger left ventricular cavity than other competitive athletes. Finally, the possibility arises that absolute posterior wall thickness may be helpful in distinguishing "athlete's heart" from hypertrophic cardiomyopathy. Indeed, in our study, the mean value for thickness of the posterior free wall of the left ventricle was slightly greater in the athlete group than in patients with hypertrophic cardiomyopathy. The substantial overlap, however, between athletes and patients prohibits the use of this variable to distinguish physiological hypertrophy from hypertrophic cardiomyopathy in individual athletes. Hence, all the diagnostic approaches described have practical and methodological considerations that limit their usefulness in differentiating physiological from pathological wall thickening in individual athletes.

For these reasons, we considered the possibility that other non-invasive diagnostic tests might aid in the differentiation of "athlete's heart" from hypertrophic cardiomyopathy. Doppler echocardiographic assessment of left ventricular diastolic filling has been shown to be abnormal in most symptom free, as well as symptomatic, patients with hypertrophic cardiomyopathy,[15] and also in patients with various other cardiac diseases.[13 17 18] Therefore, we chose Doppler echocardiography to compare left ventricular filling in competitive athletes who have considerable physiological hypertrophy with symptom free patients who have non-obstructive hypertrophic cardiomyopathy and mild pathological hypertrophy. These two groups were intentionally selected to be similar for wall thickness and age.[36] Despite these similarities, each of the 16 athletes had a normal pattern of left ventricular filling, whereas more than 80% of the patients with hypertrophic cardiomyopathy had an abnormal filling pattern. Therefore, an abnormal Doppler diastolic waveform in an athlete with considerable left ventricular hypertrophy would strongly suggest the presence of hypertrophic cardiomyopathy, whereas a normal Doppler filling pattern does not exclude the diagnosis of hypertrophic cardiomyopathy.[15 20]

The athletes, as a group, had slightly slower heart rates than either normal subjects or patients with hypertrophic cardiomyopathy. There is, however, no evidence suggesting that such a modest difference in heart rate could have accounted for the differences in early diastolic peak flow velocity between these two groups. Whereas alterations in the transmitral flow velocity waveform have been reported to be associated with increased heart rate, these changes were elicited under non-physiological conditions (that is, with intracardiac or transoesophageal pacing)[37 38] and may not be applicable to the small differences in resting heart rate found under physiological conditions in our subjects. Moreover, these reported rate related alterations in the transmitral waveform consisted mostly of increases in the late diastolic flow velocity, by contrast with the differences in early flow velocity that we found between athletes and patients with hypertrophic cardiomyopathy.

This study was supported in part by grant HL 01984 from the National Institutes of Health, Bethesda, Maryland.

1 Adams TD, Yanowitz FG, Fisher AG, Ridges JD, Lovell K, Pryor TA. Noninvasive evaluation of exercise training in college-age men. *Circulation* 1981;64.958–65
2 Sugishita Y, Koseki S, Matsuda M, Yamaguchi T, Ito I. Myocardial mechanics of athletic heart in comparison with diseased hearts *Am Heart J* 1983;105:273–80.
3 Panidis IS, Kotler MN, Ren JF, Mintz GS, Ross J, Kalman P. Development and regression of left ventricular hypertrophy. *J Am Coll Cardiol* 1984;3 1309–20.
4 Hutson TP, Puffer JC, MacMillan W. The athlete heart syndrome. *N Engl J Med* 1985;313:24–32.
5 Lusiani L, Ronsisvalle G, Bonanome A, *et al*. Echocardiographic evaluation of the dimensions and systolic properties of the left ventricle in freshman athletes during physical training *Eur Heart J* 1986;7:196–203.
6 Colan SD, Sanders SP, Barow KM Physiologic hypertrophy: effects on left ventricular systolic mechanics in athletes. *J Am Coll Cardiol* 1987;9:776–83.
7 Maron BJ. Structural features of the athlete heart as defined by echocardiography. *J Am Coll Cardiol* 1986;7:190–203
8 Douglas PS, O'Toole ML, Hiller WDB, Reichek N. Left ventricular structure and function by echocardiography in ultraendurance athletes. *Am J Cardiol* 1986;58 805–9.
9 Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991,324: 295–301.
10 Rost R. The athlete's heart. *Eur Heart J* 1982;3(suppl A): 193–8.
11 Maron BJ, Gottdiener JS, Epstein SE Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide angle, two-dimensional echocardiographic study of 125 patients. *Am J Cardiol* 1981,48·418–28.
12 Spirito P, Maron BJ, Bonow RO, Epstein SE. Severe functional limitation in patients with hypertrophic cardiomyopathy and only mild localized hypertrophy. *J Am Coll Cardiol* 1986;8:537–44.
13 Rokey R, Kuo LC, Zogbi WA, Limacher MC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with cineangiography. *Circulation* 1985,71: 543–50.
14 Gardin JM, Rohan MK, Davidson DM, *et al*. Doppler transmitral flow velocity parameters. relationship between age, body surface area, blood pressure and gender in normal subjects. *American Journal of Noninvasive Cardiology* 1987;1.3–10.
15 Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;10.743–7.
16 Spirito P, Maron BJ. Doppler echocardiography for assessing left ventricular diastolic function. *Ann Intern Med* 1988;**109** 122–6.
17 Philips RA, Coplan NL, Krakoff LR, *et al*. Doppler echocardiographic analysis of left ventricular filling in treated hypertensive patients. *J Am Coll Cardiol* 1987,9:317–22.
18 Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow-velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study *J Am Coll Cardiol* 1988;12: 426–40.
19 Bryg RJ, Pearson AC, Williams GA, Labovitz AJ Left ventricular systolic and diastolic flow abnormalities determined by Doppler echocardiography in obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 1987;59. 925–31.
20 Gardin JM, Dabestani A, Glasgow GA, Butman CS, Henry WL. Echocardiographic and Doppler flow observations in obstructed and nonobstructed hypertrophic cardiomyopathy. *Am J Cardiol* 1985;56:614–21.
21 Colan SD, Sanders SP, MacPherson D, Borow KM. Left ventricular diastolic function in elite athletes with physiologic cardiac hypertrophy *J Am Coll Cardiol* 1985; 6:545–9.
22 Granger CB, Karimeddini MK, Smith VE, Shapiro HR, Katz AM, Riba AL. Rapid ventricular filling in left ventricular hypertrophy. I. Physiologic hypertrophy. *J Am Coll Cardiol* 1985;5:862–8.
23 Pearson AC, Schiff M, Mrosek D, Labovitz AJ, Williams GA. Left ventricular diastolic function in weight lifters. *Am J Cardiol* 1986;58:1254–9.
24 Fagard R, Van den Broeke C, Bielen E, Vanhees L, Amery A. Assessment of stiffness of the hypertrophied left ventricle of bicyclists using left ventricular inflow Doppler velocimetry. *J Am Coll Cardiol* 1987;9:1250–4.
25 Finkelhor RS, Hanak LJ, Bahler RC Left ventricular filling in endurance-trained subjects. *J Am Coll Cardiol* 1986;8: 289–93
26 Maron BJ, Bodison SA, Wesley YE, Tucker E, Green KJ. Results of screening a large group of intercollegiate competitive athletes for cardiovascular disease. *J Am Coll Cardiol* 1987;10:1214–21.
27 Maron BJ, Nichols PF, Pickle LW, Wesley YE, Mulvihill JJ. Patterns of inheritance in hypertrophic cardiomyopathy: assessment by M-mode and two-dimensional echocardiography. *Am J Cardiol* 1984,53:1087–94.
28 Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasound imaging of the heart and great vessels: technique, image orientation, structure identification and validation *Mayo Clin Proc* 1978;53: 271–303.
29 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography· results of a survey of echocardiographic measurements. *Circulation* 1978,58:1072–83.
30 Spirito P, Maron BJ, Verter J, Merrill JS. Reproducibility of Doppler echocardiographic measurements of left ventricular diastolic function. *Eur Heart J* 1988;9:879–86.
31 Snedecor GW, Cochran WG. *Statistical methods*. 8th ed. Ames, Iowa: Iowa State University Press, 1989.55–7.
32 Maron BJ, Bonow RO, Cannon RO, Leon MB, Epstein SE Hypertrophic cardiomyopathy: interrelations of clinical manifestation, pathophysiology and therapy. *N Engl J Med* 1987;316:780–9, 844–52.
33 Maron BJ, Roberts WC, McAllister HA, Rosing DR, Epstein SE Sudden death in young athletes *Circulation* 1980;62 218–29.
34 Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. *J Am Coll Cardiol* 1986;7 204–14
35 Ehsani AA, Hagberg JM, Hickson RC. Rapid changes in left ventricular dimensions and mass in response to physical conditioning and deconditioning. *Am J Cardiol* 1978,42: 52–6.
36 Spirito P, Maron BJ. Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 1988;59·672–9.
37 Harrison MR, Clifton D, Pennell AT, DeMaria AN. Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. *Am J Cardiol* 1991;67·622–7.
38 Herzog CA, Elsperger J, Manoles M, Murakami M, Asinger R. Effect of atrial pacing on left ventricular diastolic filling measured by pulsed Doppler echocardiography [abstract] *J Am Coll Cardiol* 1987;9:197A.

REFLECTING QUALITY
WORLDWIDE

BSI
REGISTERED FIRM
BS 5750 (Part 2)/
ISO 9002/EN 29002
Certificate Number: FM 14713

Relied upon by leading surgeons, Swann-Morton blades are as worldwide as their reputation for quality.

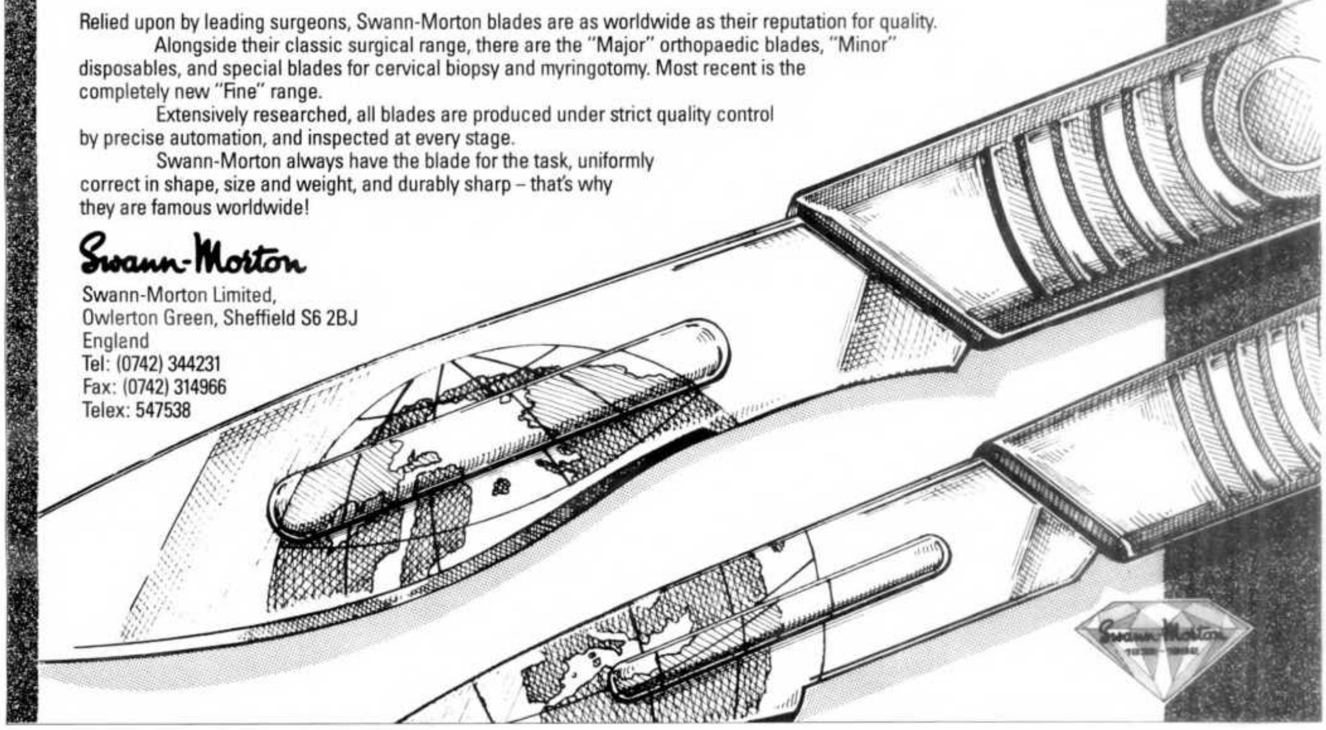
Alongside their classic surgical range, there are the "Major" orthopaedic blades, "Minor" disposables, and special blades for cervical biopsy and myringotomy. Most recent is the completely new "Fine" range.

Extensively researched, all blades are produced under strict quality control by precise automation, and inspected at every stage.

Swann-Morton always have the blade for the task, uniformly correct in shape, size and weight, and durably sharp – that's why they are famous worldwide!

Swann-Morton

Swann-Morton Limited,
Owlerton Green, Sheffield S6 2BJ
England
Tel: (0742) 344231
Fax: (0742) 314966
Telex: 547538



For your copy of the

BMJ

Book Catalogue

write now to

Books Marketing Department,
British Medical Journal, BMA House,
Tavistock Square, London WC1H 9JR.

INSTITUTE OF CHILD HEALTH
(University of London)
HOSPITALS FOR SICK CHILDREN

PULMONARY HYPERTENSION IN CHILDREN

21–22 October 1992

This course will be of interest to all paediatricians, particularly those with a neonatal or respiratory interest, and to paediatric cardiologists.

For further details please contact:

Short Courses Office
Institute of Child Health
30 Guilford Street, London WC1N 1EH
Telephone: 071 829 8692 (direct line) Fax: 071 831 0488

Two new major studies further reinforce the benefits of 'Innovace' in heart-failure treatment

Live longer...

... than patients treated with conventional therapy or a vasodilator combination. Three major survival studies involving over 3,600 heart-failure patients confirm that the addition of 'Innovace' to optimal diuretic/digoxin treatment can significantly improve survival in mild, moderate and severe heart failure when compared with placebo[1,2] or a vasodilator combination[3]

Live better...

... than patients receiving optimal diuretic/digoxin therapy. In the CONSENSUS and SOLVD studies, patients with heart failure who received 'Innovace' in addition to concomitant heart-failure treatment showed further improvements as reflected in the reduced frequency of hospitalisations[1,2]

Only

INNOVACE®

(enalapril maleate, MSD)

CONSENSUS•SOLVD•V-HeFT II

Proving to be essential in mild, moderate and severe heart failure

08-93 RNT.91.GB.25351.J.

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

INDICATIONS

All grades of essential hypertension and renovascular hypertension. Congestive heart failure (adjunctive therapy).

DOSAGE AND ADMINISTRATION

Hypertension: Initially, 5 mg once daily, reduce starting dose to 2.5 mg if over 65 years, on diuretics or renally impaired. Adjust dose according to response; maintenance usually 10-20 mg once daily. Maximum dose 40 mg daily.

Diuretic-treated patients – if possible stop diuretic two to three days before starting 'Innovace'. Resume diuretic later if required.

Congestive heart failure (adjunctive therapy): Initially, 2.5 mg daily in hospital under medical supervision, increasing to the usual maintenance dose of 10-20 mg once daily according to response.

Impaired renal function: May require a lower maintenance dose. 'Innovace' is dialysable.

CONTRA-INDICATIONS

Pregnancy – stop therapy if suspected. Hypersensitivity to 'Innovace'. Patients reacting with angioneurotic oedema to previous ACE-inhibitor treatment.

PRECAUTIONS

Assess renal function prior to therapy with 'Innovace' and during therapy where appropriate.

Renal insufficiency; possibility of hypotension especially in ischaemic heart disease or cerebrovascular disease or in volume-depleted patients; surgery/anaesthesia.

Combination with antihypertensives may increase hypotensive effect. In some patients with bilateral renal artery stenosis increased blood urea and creatinine has been seen, especially in patients treated with diuretics and/or those with renal insufficiency. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics, and potassium-containing salt substitutes are not recommended.

Possible reduced response in Afro-Caribbean patients. Use with caution in breast-feeding mothers. Do not use in aortic stenosis, or outflow tract obstruction. Monitor serum levels of lithium, if lithium salts are given.

SIDE EFFECTS

Side effects include: dizziness, headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, cough.

Less commonly, angioneurotic oedema; other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); hyperkalaemia, hyponatraemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Innovace'); paraesthesiae; impotence.

BASIC NHS COST

2.5 mg tablets, £10.00 for bottles of 50. 5 mg tablets, £7.86 for 28-day calendar pack; £14.03 for bottles of 50. 10 mg tablets, £11.03 for 28-day calendar pack; £19.69 for bottles of 50. 20 mg tablets, £13.10 for 28-day calendar pack; £23.40 for bottles of 50.

Product licence numbers:

2.5 mg tablets, 0025/0220; 5 mg tablets, 0025/0194; 10 mg tablets, 0025/0195; 20 mg tablets, 0025/0196.

Issued August 1991.

® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA

References

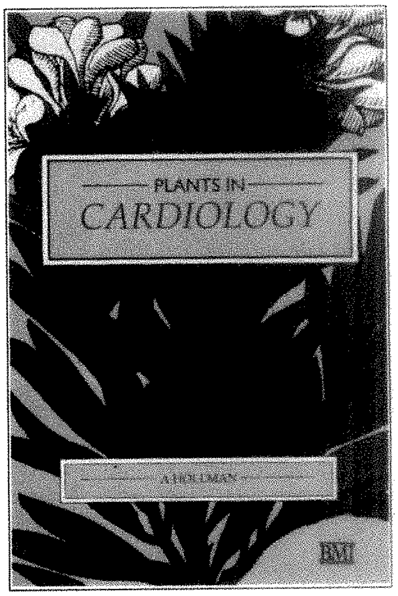
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, **63**, 26D.
2. The SOLVD Investigators, *New Engl. J. Med.*, 1991, **325**, 293.
3. Cohn, J. N., *et al.*, *New Engl. J. Med.*, 1991, **325**, 303.

MSD
MERCK SHARP & DOHME

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU

A beautiful record of cardiological discovery

In the development of modern cardiological drugs chance observation, intense prolonged chemical investigation, studies of disease in animals, and patients' own findings have all played a part, and Arthur Hollman's account of these discoveries makes fascinating reading. A keen amateur botanist who is also a member of the Committee of Management of the Chelsea Physic Garden, and a Fellow of the Linnean Society, Dr Hollman has woven medical and botanical information into succinct and elegantly written articles. His book will be of great value to everyone who is interested in nature's contribution to medicine, including cardiologists, doctors, pharmacists, botanists, herbalists and medical historians.



UK £5.95; Abroad £7.50 (BMA members £5.45 or £7.00) including postage, by air abroad

Available from BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE, *major booksellers or the BMJ bookshop in BMA House.* Book tokens accepted (UK only)

Please send me ________ copy/ies of **Plants in Cardiology**

NAME ________

ADDRESS ________

____

________ POST CODE ________

I enclose ________ BMA Membership No ________

Please make cheques payable to **British Medical Journal.**

Debit my credit card (please tick box)

☐ Visa ☐ American Express ☐ Mastercard

Card No. ________

Card expiry date ________

Signature ________

☐ Please send me a book catalogue

Essential handbook of vascular diseases

Vascular problems are common – so much so that they are often forgotten and sometimes overlooked – and the incidence of vascular disease has increased to epidemic proportions. But along with this increase has come the rapid development of new methods of diagnosis and treatment. Successful management now requires cooperation among many hospital specialists – vascular surgeons, general surgeons, radiologists, neurologists, cardiologists, orthopaedic surgeons, and general physicians – as well as paramedical staff. A key figure in the equation is the general practitioner, who has a vital part to play throughout. The *ABC of Vascular Diseases* draws together the contributions of all these, condensing years of experience into brief chapters with clear practical messages. Aspects covered include the assessment of severity of disease and medical and radiological treatment as well as surgery. Both early and late complications are covered in detail, making this an essential handbook for everyone concerned in the treatment and rehabilitation of patients with vascular disease.

Published June 1992

UK £12.95; Abroad £15.00
BMA members £11.95 or £14.00
including postage, by air abroad

Available from: **BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE,** *medical booksellers or the BMJ bookshop in BMA House*

Please send me ______ copy/ies of
ABC OF VASCULAR DISEASES

I enclose ______ Please make cheques payable to **British Medical Journal**

Debit my credit card (please tick box)
☐ Visa ☐ American Express ☐ Mastercard

Card No ______

Card expiry date ______

Signature ______

BMA Membership No ______

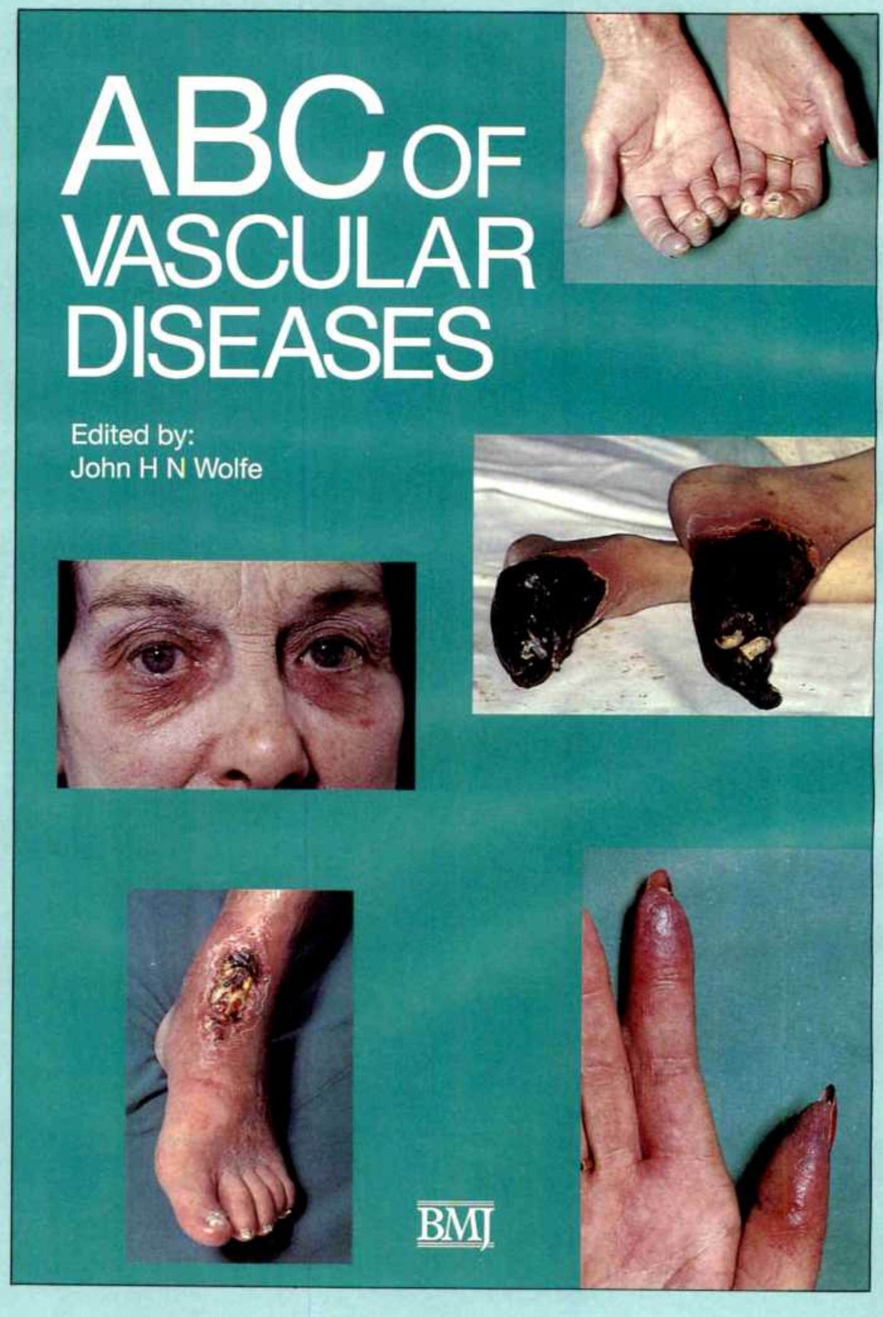
NAME ______

ADDRESS ______

______

______ POSTCODE ______

☐ Please send me a BMJ book catalogue
Book tokens accepted (UK only)



Br Heart J 1992;68:301-3

Protrusion of the device: a complication of catheter closure of patent ductus arteriosus

J Ottenkamp, J Hess, M D Talsma, T N Buis-Liem

Department of Paediatric Cardiology, University Hospital, Leiden, The Netherlands
J Ottenkamp
TN Buis-Liem

Department of Cardiology, Sophia Children's Hospital, Rotterdam, The Netherlands
J Hess

Department of Paediatric Cardiology, University Hospital, Groningen, The Netherlands
MD Talsma

Correspondence to.
Dr J Ottenkamp,
Department of Paediatric Cardiology, University Hospital Leiden, PO Box 9600-2300 RC-Leiden, The Netherlands.

Accepted for publication
8 October 1991

Abstract

Objective—To assess the medium term results of percutaneous transvenous closure of patent ductus arteriosus, in particular with regard to protrusion of the device with or without turbulence of the bloodflow.

***Design*—Clinical examination and echocardiographic study (cross sectional Doppler, and colour Doppler examination) within 24 hours of and at least 6 months after implantation (range 6–26 (mean 15) months).**

***Setting*—Multicentre study at the departments of paediatric cardiology of three academic hospitals. Tertiary clinical care of the first group of patients in the Netherlands treated by the percutaneous transvenous method.**

***Patients*—36 patients (12 male, 24 female) mean age 8·2 years, (range 1·7–58·3), mean weight 25·5 kg (range 11–67·8 kg). The total group consisted of 46 patients. In one the implantation had failed and nine others were not available for regular follow up. All 36 patients underwent non-surgical closure of the patent ductus arteriosus with a Rashkind double umbrella prosthesis.**

***Main outcome measures*—Diagnosis or exclusion of protrusion of the Rashkind device with or without turbulence of the blood flow with follow up of changes in protrusion and turbulence.**

***Results*—In 17 patients the prosthesis protruded into an arterial lumen: the aorta in 13 and the (left) pulmonary artery in four, with turbulence in seven and two cases respectively. After six months the aortic protrusion disappeared in three, including one who had had turbulent blood flow. At the end of follow up the prosthesis still protruded into the aorta in 10 but in three the turbulence had vanished. In two of the three remaining patients with turbulence in the descending aorta the degree of turbulence had decreased. There was no lessening of turbulence in the four patients in whom the device protruded into the pulmonary artery.**

***Conclusions*—The Rashkind double umbrella can protrude into the descending aorta and the left pulmonary artery without causing turbulent blood flow. Turbulence and the protrusion itself can disappear. Endocarditis prophylaxis may be required for as long as the device causes turbulence.**

(*Br Heart J* 1992,68.301–3)

Many centres use transvenous placement of the double umbrella occlusion device,[1] to close a persistently patent ductus arteriosus. Transcatheter closure is feasible in most children with a patent ductus arteriosus.[2] It is safe and effective,[3] and offers several advantages, but it is not without complications. Residual left to right shunting after incomplete closure of the patent duct was reported in more than 30% of patients.[3 4] With subsequent spontaneous closure of these often tiny, residual ductal leaks resulted in an incomplete closure rate of about 20% a year or more after the procedure.[3-5] Arterial complications sometimes require intravenous heparin.[6] Embolisation of the device, which was reported in 15% of the patients,[1] has become an uncommon event with increasing experience and improved techniques.[5 7 8] Post-implantation haemolysis is a serious complication that calls for surgical removal of the device[7] or placement of a second occluder device.[9] Both reduce one of the main advantages of the procedure—that is, a short hospital stay.[2 6] Only in one case endarteritis has been attributed to the procedure.[3] Though it has been claimed that the occluder device does not obstruct the aorta or the (left) pulmonary artery,[2] narrowing of the left pulmonary artery related to occluder device placement has been described.[3] We report on the extent of obstruction that was caused by the device in the left pulmonary artery and the descending aorta.

Patients and methods

Between February 1988 and November 1989 non-surgical closure of a persistently patent ductus arteriosus was attempted in 46 patients in three academic hospitals in the Netherlands.[8 9] Informed consent was obtained from all parents and/or patients. The treatment protocol was approved by the Ethical Review Committee of the Leiden University Hospital. The patients were not consecutive because during the study period three children were treated surgically. In one patient the procedure failed because the occluder device embolised into the right pulmonary artery. Nine patients (eight from abroad) were not available for the regular follow up, which included clinical examination, cross sectional echocardiography, and colour coded Doppler flow study.

Thirty six patients (21 from Leiden, 13 from

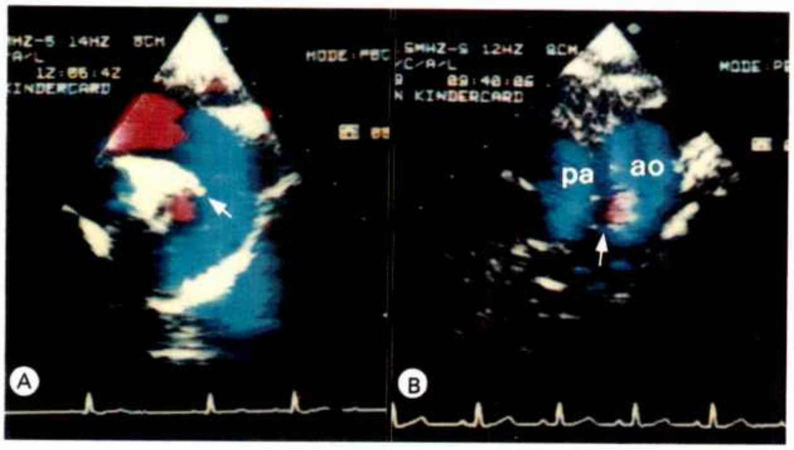


Figure 1 (A) Rashkind occluder device (arrow) protruding into the descending aorta. (B) Colour coded Doppler echocardiogram showing turbulence of flow at the inner wall of the descending aorta. The arrow points to the site of the Rashkind device. ao, descending aorta; pa, pulmonary artery.

Rotterdam, and two from Groningen) participated in the study (mean age 8·2 years, range 1·7–58·3 with four >15 years old and mean weight 25·5 kg (range 11–67·8 kg). There were 12 male and 24 female patients. One also had a small ventricular septal defect and another had serious kyphoscoliosis. We used a 12 mm diameter device in 20 patients and a 17 mm diameter device in 16 according to the echocardiographically measured and angiocardiographically verified smallest diameter of the patent duct (12 mm device if <4 mm). In three patients a second device had to be implanted; in two patients after 15 and 20 months because of a considerable residual ductal leak and in the remaining patient after seven months because of a severe haemolysis that resolved subsequently.

All 36 patients underwent a complete cross sectional echocardiographic investigation (including colour coded Doppler flow) within 24 hours of the procedure and also at least six months afterwards. We used a Hewlett Packard Sonos 1000 or a Vingmed 750 system. All but three were followed up for more than six months and were restudied at the end of the follow-up period (mean 15 months; range 6–26 months). We especially studied the aortic arch, descending aorta, pulmonary artery, and ductus arteriosus from the suprasternal and high left parasternal short axis views and the colour coded Doppler derived turbulent flow patterns caused when the always readily visualised Rashkind occluder device protruded into the lumen of the descending aorta or pulmonary artery. We used colour flow mapping to investigate residual ductal shunting.[3, 10]

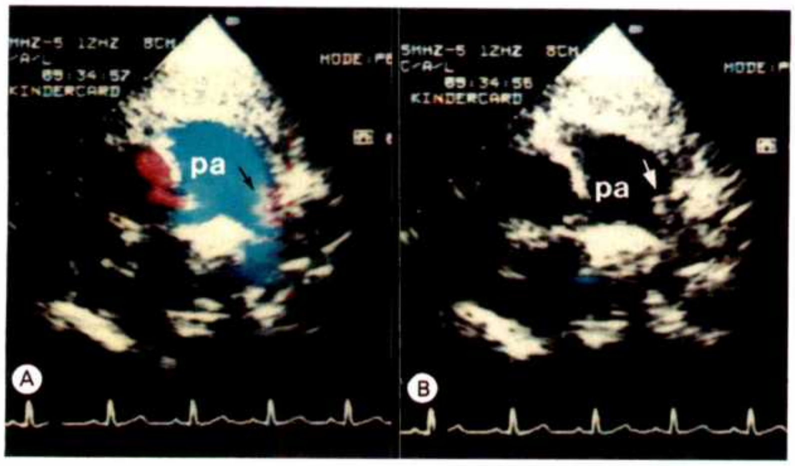


Figure 2 (A) Occluder device protruding into the left pulmonary artery (arrow). (B) Turbulence of the blood flow at the site of protrusion of the Rashkind device inside the left pulmonary artery (arrow). pa, pulmonary artery.

Results

In 13 (36%) patients the occluder device protruded into the descending aorta (fig 1A), and caused turbulent blood flow in seven (fig 1B). In six no turbulence was detected by colour coded flow imaging though the device clearly protruded. The turbulent blood flow was restricted to the inner wall of the descending aorta and was caused by one of the arms of the distal part of the device impinging on the aortic lumen. It was always unequivocally and reproducibly present. Turbulent blood flow was not seen when there was no obvious protrusion of the device. However, in several patients who had a duct with a clear aortic ampulla we found normal velocity flow towards the transducer inside the aortic end of the duct. As expected, none of the femoral arterial pulses were weakened. After six months of follow up protrusion of the device into the descending aorta had disappeared in three patients including one in whom blood flow had been turbulent. At the end of the follow up period, the device protruded into the aorta in 10 patients, but in another three patients the turbulent blood flow that had been present was no longer found. In two of the three patients with turbulent aortic blood flow at the end of the follow up period, the degree and extent of the disturbance had clearly lessened since the six month follow up. In six patients the protrusion was caused by a 17 mm device and in four it was caused by a 12 mm occluder. Protrusion of the device into the left pulmonary artery was seen in four (11%) patients (fig 2A) and this was accompanied by turbulence in two of them (fig 2B). Both had a second 17 mm device implanted. In one of them, a two year old boy weighing 12 kg, the maximal blood flow velocity measured in the left pulmonary artery was 2·7 m/s, suggesting a gradient of approximately 25 mm Hg between the main pulmonary artery and the left branch caused by the Rashkind occluder device.

The four patients in whom a portion of the occluder device protruded into the left pulmonary artery at the start of the study showed no change over time.

In eight (22%) patients we found residual ductal leaks. Two of them, mentioned before, with a haemodynamically significant residual shunting, underwent successful placement of a second occluder device and in two other patients the tiny leaks had disappeared six and 12 months later. The remaining four patients still have tiny residual ductal leaks and none of them have protrusion of the occluding device into an arterial lumen.

Discussion

Catheter closure of a patent ductus arteriosus, was successful in 80% of patients after first treatment and in over 90% when successful placement of a second device in those with considerable residual ductal leaking was taken into account.[9] Protrusion of a portion of the occluder device into the left pulmonary artery was described in a patient with an estimated gradient of 10 mm Hg.[3] Musewe *et al* described how the proximal arms of the device straddled the orifice of the left pulmonary artery in several patients but they did not report any gradient.[4] In our group of 36 patients we saw protrusion of the device into the pulmonary artery in four, with a gradient of approximately 25 mm Hg in one. During the follow up period there was no change in the numbers with narrowing of the left pulmonary artery or the extent of narrowing caused by the Rashkind occluder device. Surprisingly, we found that in 13 of the 36 patients the device protruded into the descending aorta. To the best of our knowledge, this complication has not been described before. The device seemed especially likely to protrude if a 17 mm diameter device was implanted in a small child. Protrusion of the device into the aortic lumen is most likely to occur in small children with a short duct who do not have an aortic ductal diverticulum to anchor the distal arms of the umbrella. Unlike the protrusion of the device into the left pulmonary artery, the aortic protrusion disappeared in three patients and in others the extent of turbulence caused by the device also decreased. Blood flow in the descending aorta was turbulent in seven patients shortly after insertion and in only three at the end of the follow up period. In two of these the extent of the turbulence had decreased. The suggested process of endothelialisation and covering with tissue of the discs of the double umbrella occluder device, leading to complete incorporation into the arterial walls,[1 7] is likely to be slow and gradual. Our findings accord with the suggestion that with time incorporation of the device is complete, but further follow up is needed to confirm this. How long after successful and complete closure of the patent ductus arteriosus (established by colour Doppler examination) can endocarditis prophylaxis be stopped? Some advise six months,[5] and others 12 months.[2] However, if tiny residual shunts are present or if the device protrudes into the aortic or pulmonary arterial lumen with turbulent blood flow at that site endocarditis prophylaxis should be continued.

1 Rashkind WJ, Mullins CE, Hellenbrand WE, Tait MA. Non surgical closure of patent ductus arteriosus: clinical application of the Rashkind PDA Occluder system. *Circulation* 1987,75:583–92.
2 Latson LA, Hofschire PJ, Kugler JD, Cheatham JP, Gumbiner CH, Danford DA. Transcatheter closure of patent ductus arteriosus in pediatric patients *J Pediatr* 1989; 115:549–53.
3 Dyck JD, Benson LN, Smallhorn JF, McLaughlin PR, Freedom RM, Rowe RD. Catheter occlusion of the persistently patent ductus arteriosus. *Am J Cardiol* 1988, 62:1089–92.
4 Musewe NN, Benson LN, Smallhorn JF, Freedom RM. Two-dimensional Echocardiographic and Color Flow Doppler evaluation of ductal occlusion with the Rashkind prosthesis. *Circulation* 1989;80:1706–10.
5 Ali Khan MA, Mullins CE, Nihill MR, Saad Al Yousef, Saud Al Oufy, Moheeb Abdullah, Al Fagih MR, Sawyer W. Percutaneous catheter closure of the ductus arteriosus in children and young adults *Am J Cardiol* 1989;64: 218–21.
6 Wessel DL, Keane JF, Parness I, Lock JE. Outpatient closure of the patent ductus arteriosus. *Circulation* 1988; 77·1068–71
7 Ladusans EJ, Murdoch I, Franciosi J. Severe haemolysis after percutaneous closure of a ductus arteriosus (arterial duct). *Br Heart J* 1989;61·548–50.
8 Rohmer J, Tynan M. Catheter closure of patent ductus arteriosus. *Neth J Cardiol* 1989;2:133–5.
9 Rohmer J, Hess J, Talsma MD. Sluiting van de persisterende ductus arteriosus (Botalli), door middel van catheter-interventie; de eerste 50 in Nederland behandelde patienten. *Ned Tijdschr Geneeskd* 1990;134 2347–51.
10 Ludomirsky A, O'Laughlin MP, Mullins CE. Color flow Doppler low-velocity enhancement in the assessment of residual leaks across patent ductus arteriosus occlusion devices [Abstract] *J Am Coll Cardiol* 1990,15·186.

Br Heart J 1992;68:304–8

Subclinical cardiomyopathy in Becker muscular dystrophy

Stephen E Steare, Victor Dubowitz, Avram Benatar

Abstract

***Objective*—To investigate the prevalence, age distribution, and spectrum of cardiac involvement in a cohort of patients with Becker muscular dystrophy.**

***Design*—A prospective non-invasive study with clinical, electrocardiographic, and echocardiographic assessment.**

***Patients*—19 patients (age range 16–41 years) with Becker muscular dystrophy attending the Muscle Clinic at Hammersmith Hospital and 22 healthy controls (age range 22–36 years).**

***Results*—17 patients (89%) were symptom free; two had exertional dyspnoea. Three had a past history of acute pericarditis. The electrocardiogram was abnormal in 14 patients (74%). Intraventricular conduction delay or right bundle branch block was present in eight (42%). Three (16%) had tall R waves ($R/S > 1$) in lead V1 in the absence of right bundle branch block and eight (42%) had Q waves in the lateral and inferolateral leads. The PQ interval was significantly shorter in patients with Becker muscular dystrophy ($p < 0{\cdot}01$). Echocardiography showed left ventricular dilatation in seven patients (37%) and 12 (63%) had subnormal systolic function caused by global hypokinesia (fractional shortening $<27\%$). Six of these patients were under the age of 22 years. Patients with Becker muscular dystrophy had significant reduction of both fractional shortening and corrected mean velocity of circumferential shortening compared with controls. No correlation was found between fractional shortening and age.**

The third filling fraction was significantly reduced in patients with Becker muscular dystrophy ($p < 0{\cdot}05$), although other indices of diastolic function (isovolumic relaxation time and E/A ratios) were not significantly different.

***Conclusions*—Though most patients with Becker muscular dystrophy were symptom free, a high percentage had evidence of a subclinical cardiomyopathy. Electrocardiography showed that the inferolateral and posterior segments of the left ventricle tended to be affected and may show evidence for conduction tissue disease. Echocardiography showed that most patients had left ventricular dilation and global hypokinesia. The severity of left ventricular disease was unrelated to age; some younger patients had severe left ventricular dysfunction. All patients with Becker muscular dystrophy should have echocardiographic assessment of left ventricular function.**

(*Br Heart J* 1992;68:304–8)

Becker muscular dystrophy is an X-linked recessive neuromuscular disease characterised by progressive muscular weakness. It tends to run a milder course than Duchenne muscular dystrophy with patients remaining ambulant beyond the age of 16 years and usually surviving past the age of 30 years.[1]

Gene mutations at the p21 band of the short arm of the X chromosome, coding for the protein dystrophin, are found in both Duchenne and Becker muscular dystrophy. In Duchenne muscular dystrophy there is little or no dystrophin whereas in Becker muscular dystrophy it is present in reduced quantity or is of abnormal molecular structure or both.[1]

Cardiac involvement in Becker muscular dystrophy was first recognised in 1966[2] and since then dilated cardiomyopathy has been reported in patients with this disease.[3,4] Most patients are free of cardiac symptoms.[5] A previous prospective study of 14 patients found some evidence of cardiac involvement in 64%; however, none had a dilated cardiomyopathy.[6] Myocardial involvement in Becker muscular dystrophy seems to be unrelated to the clinical severity or duration of skeletal muscle involvement[4] and may even precede the onset of muscle weakness.[7] Evidence of cardiac involvement may be found on electrocardiography. Described abnormalities include intraventricular and right bundle branch blocks,[4,5]; ST segment abnormalities[8]; T wave abnormalities[3,8,9]; and Q waves in the inferior,[8] lateral,[7–9] and precordial[8] leads. The PQ segment (end of P wave to beginning of QRS) is shortened and the QT/PQ ratio (cardiomyopathic index) is increased in both Becker and Duchenne muscular dystrophy.[10] These changes are believed to be useful electrocardiographic indicators of early cardiac involvement.[10] Thallium perfusion studies in patients with Becker muscular dystrophy with dilated cardiomyopathy identified regional perfusion defects in the left ventricle in the absence of coronary artery disease.[11,12]

The pathology of the dilated cardiomyopathy in Becker muscular dystrophy consists of diffuse degeneration and fibrosis of both

Department of Medicine (Cardiology) and Neuromuscular Unit, Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London
S E Steare
V Dubowitz
A Benatar

Correspondence to
Dr Avram Benatar,
Department of Cardiology,
Wilhelmina
Kinderziekenhuis, P.O. Box
18009, 3501 CA Utrecht,
Netherlands.

Accepted for publication
18 March 1992

ventricles, especially of the mid-myocardium and the posterolateral portion of the left ventricle.[9 13] Necrosis and fibrosis of the conducting tissue have also been reported.[13]

Cardiac disease is likely to be an important determinant of functional capacity and survival in Becker muscular dystrophy because the skeletal and respiratory muscles are less severely affected than in Duchenne muscular dystrophy. Although the dilated cardiomyopathy seen in some patients may represent the end stage of progressive cardiac involvement in Becker muscular dystrophy, there are few data on the prevalence and natural history of cardiac involvement. We report the results of a cross sectional study of cardiac disease in 19 patients.

Patients and methods

We studied 19 patients attending the Muscle Clinic at Hammersmith Hospital. The research protocol was approved by the ethics committee of the Royal Postgraduate Medical School and informed consent was obtained from each patient. The specific diagnosis of Becker muscular dystrophy, as opposed to Duchenne muscular dystrophy, was made on the basis of the typical clinical features of dystrophy and the ability to walk at the age of 16 years.[14] The diagnosis was confirmed histologically on muscle biopsy. Sixteen patients had undergone genetic studies and the skeletal muscle dystrophin status had been determined in nine patients by the western blot technique. Patients were divided into three broad clinical groups according to degree of physical disability: (I) minor impairment of motor function, (II) major impairment of motor function—ambulant, (III) major impairment of motor function—wheelchair dependent. Comparative data were obtained from 22 healthy volunteers.

A detailed history was taken with particular attention to cardiovascular symptoms and drug history. A full clinical examination was performed. Pulmonary function as assessed by forced vital capacity was measured by standard spirometry and compared with standard tables.

The patients and 22 controls had 12 lead electrocardiograms recorded at speeds of 25 and 50 mm/s on a Marquette Mac 12. These were analysed for morphological, rhythm, and conduction abnormalities. The PR and QT intervals and the PQ segment were measured from standard lead II,[15] and the P/PQ and QT/PQ ratios were calculated.

Transthoracic echocardiography by M mode, cross sectional Doppler, and colour flow mapping was performed on a Toshiba SSH-160A scanner. Both 2·5 and 3·75 mHz probes were used for imaging and Doppler studies. The patients and 19 controls were examined in the left lateral position from standard parasternal and apical views, with simultaneous electrocardiogram and phonocardiogram recordings. All measurements were averaged over 3–5 cardiac cycles. Internal chamber measurements (left ventricular internal dimension in diastole and systole (LVIDd and LVIDs) and the left atrial dimension) were measured as recommended by the American Society of Echocardiography.[16] From an apical four chamber view, mitral inflow velocities were assessed with range gated pulsed Doppler echocardiography. The sample volume was positioned parallel to the flow at the site of maximum velocity at the tip of the mitral leaflets. The following were measured: left ventricular ejection time (ET), isovolumic relaxation time, RR interval, peak E and A velocities, and the velocity time integral of total diastolic filling (VTI total) and of the first third of diastolic filling (VTI third).

The following indices of systolic and diastolic function were calculated: shortening fraction ($SF = [LVIDd - LVIDs]/LVIDd$), corrected mean velocity of circumferential shortening ($mVcFc = [LVIDd - LVIDs]/LVIDd \times ETc$, where $ETc = ET/$square root of the RR interval), E/A velocity ratios (peak velocity E/peak velocity A), and third filling fraction (VTI total/VTI third).

STATISTICAL ANALYSIS

The numerical variables are expressed as mean (SD). A two-tailed, unpaired *t* test was used for statistical analysis. A p value of less than 0·05 was regarded as significant. The 95% confidence intervals are given.

Results

CLINICAL PROFILE

The patients' ages ranged from 16 to 41 years (mean 23, median 22) and those of the 22 controls from 22 to 36 years (mean 27, median 26).

Of the 19 patients, 12 had minor motor impairment (I), four had major impairment but were ambulant (II), and three were wheelchair dependent (III). The dystrophin in all nine patients studied was of a truncated form and present in reduced amounts. Of the 16 patients who underwent genetic studies, 12 had detectable deletions in the Duchenne gene and no deletions were detectable in the remaining four. Patients were divided into three groups according to the site of exon deletions in the Duchenne gene: A, exons 13–19; B, exons 9–45; and C, exons 45–49 (table 1).

Seventeen patients were free of cardiac symptoms and two had exertional dyspnoea. In the past, three patients had had acute pericarditis. Except for one patient who was taking atenolol, no one else was receiving regular medication at the time of the study. All were normotensive and none had abnormal cardiac signs.

ELECTROCARDIOGRAPHIC STUDIES

The electrocardiogram was completely normal in five patients (table 2). All patients were in sinus rhythm apart from one, who in addition had a short run of nodal rhythm. An intraventricular conduction delay including incomplete right bundle branch block was present in six patients and complete right bundle branch block occurred in two others. When patients with incomplete or complete right bundle

Table 1 *Data on patients with Becker muscular dystrophy*

Case	*Age (yr)*	*Functional grade*	*Symptoms and past history*	*Drugs*	*Exon deletions*
1	17	I	None		45–47 (C)
2	21	I	None		13 (A)
3	26	III	None		9–45 (B)
4	19	II	None		NT
5	25	II	SOB, P 22 yr		45–48 (C)
6	26	III	None		45 (C)
7	16	I	SOB		ND
8	16	I	P 15 yr		45–47 (C)
9	41	II	None		NT
10	16	I	None		NT
11	26	I	None		46–49 (C)
12	22	I	None		45–47 (C)
13	22	I	None		ND
14	26	I	None		45–47 (C)
15	39	II	None		13–19 (A)
16	25	III	P 23 yr	Atenolol	19–44 (B)
17	19	I	None		ND
18	17	I	None		ND
19	16	I	None		48 (C)

SOB, shortness of breath; P, pericarditis, I, minor motor impairment; II, major motor impairment—ambulant; III, wheelchair dependent, Exon deletion groups· A, 13–19; B, 9–45; C, 45–49; ND, no deletion detected; NT, not tested.

Table 2 *Spirometry, electrocardiography, and echocardiography in patients with Becker muscular dystrophy*

Case	*FVC (%)*	*Electrocardiogram*	*QTc (ms)*	*QT/PQ*	*LVIDd (mm)*	*FS (%)*
1	96	IRBBB	399	10 70	51	24
2	93	RBBB	408	10 20	52	21
3	42	IVCD	423	7 36	42	23
4	89	Run nodal rhythm, IVCD	410	10 01	62	15
5	77	Normal	404	8 80	47	27
6	42	Tall R V1, Lat Q & T abn	441	8 60	66	13
7	71	Tall R V1, Lat Q	409	8·25	56	22
8	NT	Tall R V1, Lat Q & R loss	432	7 36	48	26
9	78	Reduced R V2-V3	442	10·20	58	21
10	65	LAH, IRBBB, Inf-lat T abn	456	10·00	53	26
11	80	LVH	430	10 00	51	27
12	98	Normal	391	11 80	55	29
13	53	IVCD, Lat Q & T abn	444	9 75	58	15
14	98	Normal	402	18·00	55	16
15	NT	Normal	412	18 20	48	23
16	NT	Normal	386	5 25	46	32
17	100	Inf-lat Q	389	12 66	46	28
18	82	IVCD, Lat Q	388	13·86	50	29
19	82	RBBB, LVH, Lat Q	403	9 30	52	29

FVC, forced vital capacity (% predicted); LVIDd, left ventricular internal dimension in diastole; FS%, percentage left ventricular fractional shortening, IRBBB, incomplete right bundle branch block; RBBB, complete right bundle branch block; IVCD, intraventricular conduction delay; Lat, lateral; Inf-lat, inferolateral, LAH, left anterior hemiblock; LVH, left ventricular hypertrophy; NT, not tested.

branch block were excluded, pathologically tall R waves (R/S in V1 < 1) were present in three patients. In a further six, the R/S ratio in V1 $> 0·5$ mV whereas the R/S V1 ratio in controls was always $< 0·5$ mV. In four patients Q waves were seen in the lateral leads (amplitude $> 0·5$ mV in leads I and aVL) and in two of these Q waves were also present in the inferior leads (amplitude $> 0·3$ mV in leads II and aVF). A further three patients had small Q waves (0·2–0·5 mV) in the lateral leads. Q wave duration was between 20 ms and 40 ms and in only one of the seven was associated with R wave loss. One other patient had R wave voltage reduction in the anterior chest leads. T wave abnormalities were seen in three patients—associated with lateral Q waves in two and as a sole abnormality in the inferolateral leads in one other. Two patients had electrical voltage criteria for left ventricular hypertrophy without a strain pattern.

There was no significant difference in the resting heart rates or the P wave duration between the two groups. The PR and PQ intervals were significantly shorter and the QTc intervals were significantly longer in patients with Becker muscular dystrophy (table 3), however. In four patients QTc was > 440 ms, and in two of these patients had intraventricular conduction delays.

Since the effect of heart rate on the P/PQ and QT/PQ ratios has not been clearly established we compared the P/PQ and QT/PQ ratios in two heart rate bands (table 4). A patient with a resting heart rate of 100 beats/min was excluded from analysis. Significant differences in both these ratios were found between the Becker and control groups even when heart rates were matched in this way. No correlation was found between the QT/PQ or P/PQ ratios and the genetic deletion group or with left ventricular function as determined by fractional shortening.

ECHOCARDIOGRAPHIC STUDIES

No valve abnormality was detected in any individual. Left ventricular dilatation (LVIDd $> 95\%$ of the predicted upper limit for body weight) was seen in seven of the 19 patients (table 2). None of the patients had left atrial enlargement. Delayed and reduced septal wall motion was noted in two patients—one with complete right bundle branch block and another with incomplete right bundle branch block. Regional wall motion abnormalities were not seen in any of the other subjects.

Estimates of systolic function were subnormal in 12 patients (table 2). As a group, the

Table 3 *Electrocardiographic values in patients with Becker muscular dystrophy and controls*

	HR (min⁻¹)	*PR (ms)*	*P (ms)*	*PQ (ms)*	*QTc (ms)*
Becker (= 19)	73·1 (11·8)	134 1 (18 5)†	92 5 (13 9)	40 0 (12 0)†	414 2 (21 2)*
Controls (n = 22)	67 6 (11 6)	156 0 (21·1)	97·6 (14 2)	58 4 (16 4)	400 8 (18 2)
CI	−1 9 to 12 9	−34 5 to −9 4	−14 0 to 3 8	−27·6 to −9 2	0 9 to 25 8

HR, heart rate; PR, PR interval; P, P wave duration; PQ, PQ interval; QTc, QTc interval; CI, 95% confidence intervals.
*p < 0 05, †p < 0 01

Table 4 *Comparison of P/PQ and QT/PQ ratios in two heart rate bans in patients with Becker muscular dystrophy and controls*

	HR 50–70 beats/min			*HR 71–90 beats/min*		
	n	*P/PQ*	*QT/PQ*	*n*	*P/PQ*	*QT/PQ*
Becker	*7*	2 56 (0 86)*	10·40 (2·71)*	*11*	2 75 (1 12)*	10·82 (3 82)†
Controls	*9*	1 67 (0·44)	7 38 (1 84)	*11*	1 83 (0 64)	6 72 (1 59)
CI		0 18 to 1 6	0 6 to 5 45		0·11 to 1·73	1 5 to 6 7

HR, heart rate, CI, 95% confidence intervals; p < 0 05, †p < 0 01.

Table 5 Echocardiographic values in patients with Becker muscular dystrophy and controls

	FS (%)	*mVcFc (cm/s)*	*IRT (ms)*	*E/A*	*Third filling fraction*
Becker (= 19)	23·47 (5·51)†	0·78 (0·18)†	54·20 (11·1)	2·16 (0·94)	0·58 (0·13)*
Controls (n = 19)	32·89 (4·78)	1·07 (0·13)	50·79 (8·82)	2·10 (0·33)	0·67 (0·10)
CI	−12·8 to −6·0	−0·4 to −0·19	−3·2 to 10	−0·42 to 0·53	−0·17 to −0·01

FS percentage fractional shortening of the left ventricle; mVcFc, corrected mean velocity of circumferential fibre shortening; IRT, isovolumic relaxation time; E/A, E/A velocity ratio; CI, 95% confidence intervals.
$^*p < 0·05$; $^†p < 0·01$.

patients with Becker muscular dystrophy had a significantly smaller shortening fraction and corrected mean velocity of circumferential shortening than the controls (table 5).

Fractional shortening did not correlate with pulmonary function, age, the severity of skeletal muscle involvement, or the patients' gene deletion site.

The third filling fraction was significantly reduced in the Becker group, although other indices of diastolic function (isovolumic relaxation time and E/A velocity ratio) were not significantly different from values in the controls (table 5).

Discussion

The prevalence, spectrum, and timing of onset of cardiac disease in Becker muscular dystrophy has received little attention despite the recognised association with a dilated cardiomyopathy.[2-4] We found a surprisingly high frequency of electrocardiographic and echocardiographic evidence of important subclinical cardiac involvement in this condition.

The electrocardiogram was abnormal in 74% of patients, and this may be an early indicator of cardiac disease. Non-specific changes, in particular intraventricular and right bundle branch block, were frequent (42%). Others have reported these changes in patients with Becker muscular dystrophy[4 5] and they may reflect damage to the intraventricular conduction system, which is known to occur in patients with a dilated cardiomyopathy.[2 13] Such involvement may even lead to complete heart block[2] and should not be underestimated. Ambulatory electrocardiographic monitoring may provide additional information about disease of the conducting tissue in these patients. Specific changes were common (47%) and most often took the form of a "pseudo-infarction" pattern, comprising of narrow Q waves without associated R wave loss in the inferolateral leads (42%) and/or tall R waves in the right precordial leads (16%). These two types of abnormalities have been reported in patients with Duchenne muscular dystrophy[17 18] and in patients with Becker muscular dystrophy.[3 7 9] In Duchenne muscular dystrophy the histological basis for these changes is diffuse myocardial fibrosis with a tendency for early involvement of the posterobasal and adjacent free wall of the left ventricle.[17 19] It is likely that the electrocardiographic abnormalities see in Becker muscular dystrophy reflect a similar underlying disease process.

In three patients with regional electrocardiographic changes there was no demonstrable left ventricular dysfunction on echocardiography. Furthermore, in all nine patients with these abnormalities corresponding regional wall motion abnormalities were not detected. Thus the electrocardiogram may be very sensitive in detecting early ventricular pathology.

QTc prolongation was present in 16% of patients and in all four patients was associated with appreciable left ventricular dysfunction. Thus it may provide additional evidence of left ventricular disease in patients with Becker muscular dystrophy.

Nigro *et al*[10] emphasised the value of the QT/PQ ratio, the "cardiomyopathic index", as an early marker of cardiac involvement in the progressive X-linked muscular dystrophies. Our data confirm that this index and the P/PQ ratio are both increased in patients with Becker muscular dystrophy. The PQ segment was significantly shorter in Becker patients and accounts for the higher QT/PQ and P/PQ ratios. Shortening of the PQ interval and an increase of the P/PQ ratio are associated with either left atrial enlargement[20] or left atrial fibrosis.[15] Because the left atrial dimension was normal, in all of the patients studied, these electrocardiographic changes are likely to reflect left atrial fibrosis. No association was found between the QT/PQ ratio and left ventricular fractional shortening. Whereas the QT/PQ ratio may provide a useful indicator of atrial disease it should not be used alone to gauge the severity of overall cardiac involvement.

Echocardiography showed that an unexpectedly high percentage of patients (67%) had subnormal left ventricular function. In addition 31% had left ventricular dilatation. The severity of left ventricular disease was unrelated to age, and, more importantly, severe left ventricular impairment occurred in some patients in their teens and early twenties. We predict that such young patients, who often have only slight impairment of skeletal muscle, will develop congestive cardiac failure in the near future. There are considerable therapeutic implications in the management of such patients both before and after onset of cardiac symptoms. The possible benefits from the early use of vasodilator therapy in these patients will require proper evluation. Cardiac transplantation may also be an effective treatment for those patients with cardiac failure refractory to medical treatment, who would otherwise have a reasonable life expectancy.[4 13]

Left ventricular dysfunction is common in Duchenne muscular dystrophy[21 22] and it does not seem to be directly associated with respiratory impairment.[22] We also found this to be true of Becker muscular dystrophy. It seems that in Becker muscular dystrophy the onset and progression of cardiac disease bear no relation to involvement of the skeletal and thoracic cage muscles. In addition, we did not find an association between left ventricular function and the underlying deletion on the Duchenne gene. Currently there is no evidence that the type of gene deletion is predictive of the extent of cardiac involvement.

We used mitral inflow velocities to estimate the diastolic properties of the left ventricle. Abnormalities of diastolic function were expected in those patients with a cardiomyopathy because they have extensive and diffuse ventricular fibrosis.[2 13] The third filling fraction was the only index of diastolic function found to be significantly different from indices in the controls. Echocardiographic evaluation of diastolic function may be influenced by atrial disease and compliance,[23] and this may account for the discrepancy in the results. We cannot draw conclusions about ventricular compliance from this study.

Despite having considerable and often severe cardiac disease, most patients were free of cardiac symptoms. It has previously been suggested that the physical limitations imposed by the skeletal muscle disease in Duchenne muscular dystrophy protects the individual against the demands that may lead to cardiac symptoms.[21] Although some of the patients with Becker muscular dystrophy experienced severe physical limitations, most were ambulant and active and yet they remained symptom free. Dyspnoea may be the earliest symptom of cardiac failure, but it may also be caused by respiratory impairment in patients with Becker muscular dystrophy. A detailed assessment of both systems is required to elucidate the aetiology of this symptom.

Acute pericarditis occurred in 16%, a frequency that was greater than expected. In only one of the three patients was there detectable myocardial involvement. Though acute pericarditis may be more frequent in Becker muscular dystrophy, it is not clear whether it is part of the spectrum of cardiac involvement in this disease. In conclusion, this study has shown that whereas most patients with Becker muscular dystrophy are free of cardiac symptoms, subclinical cardiac disease is very common: it may be severe and it may be present in adolescence. The electrocardiogram may show that the left ventricle is affected, with early evidence of abnormalities of the posterobasal and lateral wall, left atrial fibrosis, and conduction tissue disease. The echocardiogram is essential in the assessment of left ventricular size and function. Careful follow up is required to determine the rate of progression of cardiac disease in these patients.

We thank Professor M Bobrow and colleagues (Guy's Hospital Medical School, London) and Dr P N Strong and Dr Caroline Sewry (Neuromuscular Unit Laboratories, Royal Postgraduate Medical School) for the deletion studies and dystrophin analyses, respectively.

1 Darras BT. Molecular genetics of Duchenne and Becker muscular dystrophy. *J Pediatr* 1990,117·1–15.

2 Perloff JK, Deleon AC, O'Doherty D. The cardiomyopathy of progressive muscular dystrophy. *Circulation* 1966, 33:625–58.

3 Katiyar BC, Misra S, Somani PN, Chaterji AM. Congestive cardiomyopathy in a family of Beckers X-linked muscular dystrophy *Postgrad Med J* 1977;53:12–5.

4 Sakata C, Yamada H, Sunohara N, Arahara K, Nonaka I Cardiomyopathy in Becker muscular dystrophy. *Rinsho Shinkeigaku* 1990,30:952–5.

5 Emery AEH, Skinner R. Clinical studies in benign (Becker type) X-linked muscular dystrophy. *Clin Genet* 1976; 10:189–201

6 Nigro G, Limongelli FM, Grugliano M-AM, Politano L, Passamano L, Stefanelli S. Prospective study of X-linked progressive muscular dystrophy in Campania *Muscle Nerve* 1093;6.253–62.

7 Sakata C, Sunohara N, Nonaka I, Arahata K, Sugita H A case of Becker muscular dystrophy presenting as cardiac failure as an initial symptom. *Rinsho Shinkeigaku* 1990; 30 210–3.

8 Markand ON, North RR, D'Agostino AN, Daly DD. Benign sex linked muscular dystrophy. *Neurology* 1969, 19:617–33.

9 Ueda K, Okada R, Matsuo H, Hamurni K, Yasuda H, Tsyuki H, Ueda H Myocardial involvement in benign Duchenne type of muscular dystrophy. *Jap Heart J* 1970;11.26–35.

10 Nigro G, Comi LI, Politano L, *et al*. Electrocardiographic evaluation of the P type stage of dystrophic cardiomyopathy. *Cardiomyology* 1984;3.45–58

11 Levin RN, Nahara KA Right axis deviation and anterior wall thallium-201 defect in Becker's muscular dystrophy *Am J Cardiol* 1985,56:203–4.

12 Lazzeroni E, Favaro L, Botti G Dilated cardiomyopathy with regional myocardial hypoperfusion in Becker's muscular dystrophy. *Int J Cardiol* 1989;22:126–9.

13 Donofrio PD, Challa VR, Hackshaw BT, Mills SA, Cordell R. Cardiac transplant in a patient with muscular dystrophy and cardiomyopathy. *Arch Neurol* 1989,46·705–7.

14 Hodgson S, Hart K, Abbs S, Heckmatt J, Rodillo E, Bowbrow M, Dubowitz V. Correlation of clinical and deletion data in Duchenne and Becker muscular dystrophy. *J Med Genet* 1989;26 682–93

15 Scott CC, Leier CV, Kilman JW, Vasko JS, Unverferth DV. The effect of left atrial histology and dimension on P wave morphology. *J Electrocardiol* 1983,16:363–6.

16 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantation in M mode echocardiography: Result of a survey of echocardiographic measurements *Circulation* 1978,58:1072–107

17 Perloff JK, Roberts WC, Deleon AC, O'Doherty D The distinctive electrocardiogram of Duchenne progressive muscular dystrophy. An electrocardiographic pathological correlative study *Am J Med* 1967;42:179–88.

18 Sanyal SK, Johnson WW, Thapar MK, Pitner SE. An ultrastructural basis for electrocardiographic alterations associated with Duchenne's progressive muscular dystrophy *Circulation* 1978;57 1122–48.

19 Frankel KA, Rosser RJ The pathology of the heart in progressive muscular dystrophy; epimyocardial fibrosis. *Hum Pathol* 1976;7 375–86.

20 Macruz R, Perloff JK, Case RB. A method for the electrographic recognition of atrial enlargement. *Circulation* 1958;17.882–9

21 Danilowicz D, Rutkowski M, Myung D, Schively D Echocardiography in Duchenne muscular dystrophy. *Muscle Nerve* 1980;3 298–303.

22 Stewart CA, Gilgoff I, Baydur A, Prentice W, Applebaum D Gated radionucleotide ventriculography in the evluation of cardiac function in Duchenne muscular dystrophy *Chest* 1988;94:1245–8.

23 Shapiro SM, Bersohn MM, Laks MM. In search of the holy grail: the study of diastolic ventricular function by the use of doppler echocardiography. *J Am Coll Cardiol* 1991; 17 1517–9.

Br Heart J 1992;68:309–12

Influence of cardiopulmonary bypass on water balance hormones in children

M Burch, L Lum, M Elliott, N Carter, D Slater, A Smith, A Ationu

Hospital for Sick Children, Great Ormond Street, London
M Burch
L Lum
M Elliott

St George's Hospital Medical School, London
N Carter
D Slater
A Smith
A Ationu

Correspondence to
Dr M Burch, Department of Cardiology, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH

Accepted for publication
12 March 1992

Abstract

***Objective*—To determine the changes in the endocrine mechanisms of fluid balance after cardiopulmonary bypass in children.**

***Design*—Prospective study; analysis of numbered plasma samples performed blind with respect to clinical data.**

***Setting*—Regional paediatric cardiothoracic unit.**

***Patients*—Nine patients, median age 4, range 2 to 9 years, five males. Patients under the age of 1 year were excluded because of the frequent blood sampling involved.**

***Main outcome measures*—Plasma concentrations of atrial natriuretic peptide (ANP), arginine vasopressin, plasma renin activity, aldosterone, noradrenaline and adrenaline, and urinary concentrations of cyclic guanosine monophosphate (cGMP) as measured by radioimmunoassay.**

***Results*—After 30 minutes of cardiopulmonary bypass plasma atrial natriuretic peptide (ANP) decreased from (mean (SEM)) 151 (71) pg/ml to 52 (44) pg/ml (NS), and urinary production of its second messenger cyclic guanosine monophosphate (cGMP) decreased from 1286 (600) pmol/ml to 151 (414) pmol (p < 0·05). Other plasma concentrations of hormones studied did not change significantly although arginine vasopressin, adrenaline, and noradrenaline increased whereas aldosterone and plasma renin activity decreased. After cardiopulmonary bypass stopped there was an immediate and significant rise in plasma ANP, but within the next 24 hours plasma ANP declined significantly (p < 0·05), decreasing from 294 (49) pg/ml to 64 (29) pg/ml at 22 hours. In the postoperative period there was a significant correlation between plasma ANP and both mean fluid balance (*r* = 0·96, p < 0·001) and mean urine output (*r* = 0·97, p < 0·001). Plasma aldosterone peaked (p < 0·05) at 22 hours after operation, and argine vasopressin peaked (p < 0·05) at two hours and then declined (p < 0·05) to a trough at 24 hours. Plasma renin activity, adrenaline, noradrenaline, and urinary cGMP concentrations, and mean central venous pressure did not change significantly in the postoperative period.**

***Conclusion*—The changes documented show the differing pattern of release of water balance hormones invoked by cardiopulmonary bypass. The central role of ANP is shown by its strong correlation with urinary output and its similarly strong relation to fluid balance.**

(*Br Heart J* 1992;68 309–12)

Cardiopulmonary bypass results in complex disturbances of homoeostatic mechanisms including complement activation and consumption,[1] prostaglandin production,[2] and secretion of vasopressin and catecholamines.[3] Furthermore, the metabolic response to cardiopulmonary bypass is more severe in children than in adults.[4–6] Atrial natriuretic peptide (ANP) is a recently discovered hormone secreted primarily by atrial myocytes in response to local wall stretch and seems to be important in fluid homeostasis[7]; the physiological mechanisms for its release may be exaggerated in childhood.[8] Recent studies have examined the effect of cardiopulmonary bypass on ANP in adults,[9–11] but no previous studies have documented the effect of cardiopulmonary bypass on ANP in children. We have therefore studied nine children undergoing bypass and measured plasma concentrations of ANP. Also, we have measured other water balance hormones to provide a complete assessment of the effect of cardiopulmonary bypass on the homeostatic mechansism regulating water balance as this has not been previously undertaken in either adults or children.

Patients and methods

CHARACTERISTICS OF PATIENTS

The parents of all the children involved in this study gave informed consent. The hospital ethics committee gave ethical approval.

We investigated nine patients undergoing elective cardiac surgery. Their median age was 4 (range 2 to 9) years and five were males. The surgery undertaken was: repair of atrial septal defect (three patients), repair of tetralogy of Fallot (two), repair of pulmonary atresia with ventricular septal defect with a right ventricular to pulmonary artery homograft (two), and total cavopulmonary connection (two).

ANAESTHETICS

We used a standard technique. Anaesthesia was induced with cyclopropane and oxygen, suxamethonium (1 mg/kg/IV), and pancuronium bromide (0·1 mg/kg/IV) and maintained with nitrous oxide and oxygen with intermittent pancuronium, fentanyl, or morphine.

PERFUSION AND BYPASS

A non-pulsatile roller occlusive pump maintained perfusion flow rates at 2·4 l/m^2/min except transiently.

We used a hollow fibre membrane oxygenator with integral heat exchanger and venoarterial core cooling; cardioplegia was achieved with St Thomas's No 2 solution. The pump prime had a volume of 1100–1600 ml and the crystalloid component consisted of plasmalyte A. Stored blood containing citrate, phosphate, and dextrose was added in a volume calculated (from a standard nomogram relating surface area to prime volume) to a packed cell volume of 30% on bypass; 2500 U of heparin was added to each unit of blood and 1600 U to each 500 ml of crystalloid; 8·4% sodium bicarbonate was added to provide a pH between 7 3 and 7·4.

As standard practice in our unit a Gambro FH 77 ultra filter with an effective membrane area of 1·4 m^2 was inserted between the arterial line of the bypass circuit and the cardiotomy reservoir. The system was topped up with plasmalyte A as the filtrate was formed until 1400 ml of filtrate had been discarded. This volume has been shown to produce a satisfactory reduction in the metabolic load of the pump priming fluid. Perioperative fluids consisted of plasmalyte A, plasma protein fraction, fresh frozen plasma, and blood as indicated by the clinical condition of the patient. On transfer to the intensive care unit 5% glucose in water was infused at 20 ml/m^2/hr. Potassium chloride was added to maintain plasma potassium concentrations between 4·0 and 5·0 mmol/l. Blood or plasma protein fraction were used for volume replacement to maintain a packed cell volume >35%.

BLOOD SAMPLING

Blood samples were taken from indwelling arterial cannulae after induction of anaesthesia. Previous studies have shown that the metabolic disturbances are largely complete by six hours,[1-3] but we extended the sampling period to include the first 24 hours after operation.

Samples were taken after sternotomy, at the start of bypass, every 15 minutes during bypass, and at the end of bypass. Subsequent samples were taken at two, six, 12, 16, 22, and 24 hours after the end of bypass. Blood was collected in tubes containing ethylenediaminetetracetate (EDTA), centrifuged, and plasma was removed and frozen at −70°C. As larger volumes of plasma were needed for analysis of adrenaline and noradrenaline postoperative sampling was limited to six, and 24 hours. Also, urine for cyclic guanosine monophosphate (cGMP) analysis was collected less often.

Urine output and fluid balance were expressed as ml/kg/hr, and were measured for the hour before plasma sampling, when no diuretic was given. The fluid balance represented net balance of crystalloid and colloid losses including that from chest drains, but insensible losses were not included. Mean values of urinary output and fluid balance were calculated for each sampling period.

Fluids were restricted to 50 ml/kg of crystalloid/24 hr for all patients, although colloid was given as required.

RADIOIMMUNOASSAY (RIA) PROCEDURES

Plasma atrial natriuretic peptide (ANP) and arginine vasopressin (AVP) were initially extracted in C_8 reversed phase columns (Analytichem International), and their concentrations were then measured by specific RIA as we described for ANP[8] and AVP.[12] Plasma aldosterone was assayed with a commercially available RIA kit according to the manufacturers' instructions (Biogenesis Ltd). The plasma renin activities (PRA) were determined by the method supplied by the Regional Chemical Pathology Unit, St Mary's Hospital, Paddington, London. Urinary cGMP was measured directly in urine by RIA with a commercial kit (NEN Research Products, Du Pont UK Ltd).

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

Plasma adrenaline and noradrenaline concentrations were measured by HPLC with electrochemical detection after initial extraction of plasma on alumina columns (Laboratory Impex). The system was a 114 M solvent delivery module with an injection valve fitted to a 50 μl sample loop with a stainless steel analytical column (25 cm × 4·6 mm) (Beckman), carrying a 5 cm × 4.6 mm internal diameter guard column packed with pellicular C_{18} ODS (Whatman).

The electrochemical detector was an ESA Coulochem model. The mobile phase contained 40 mM citric acid, 80 mM sodium acetate, 60 mM sodium hydroxide, 370 mg/l EDTA, 280 mg/l heptane sulphonate (ion pair reagent), and 10% methanol as organic modifier. Standard adrenaline and noradrenaline (500 pg/50 μl) and extracted plasma (50 μl) containing internal standard were injected into the HPLC system.

STATISTICAL ANALYSIS

Data are presented as mean (SEM) where appropriate and correlations were obtained by

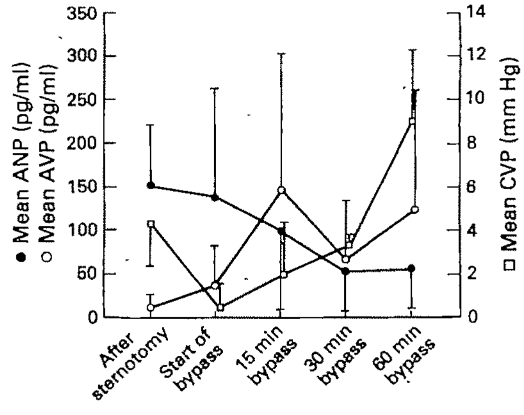


Figure 1 Changes in mean values of plasma ANP, plasma arginine vasopressin (AVP), and central venous pressure (CVP) against time during bypass

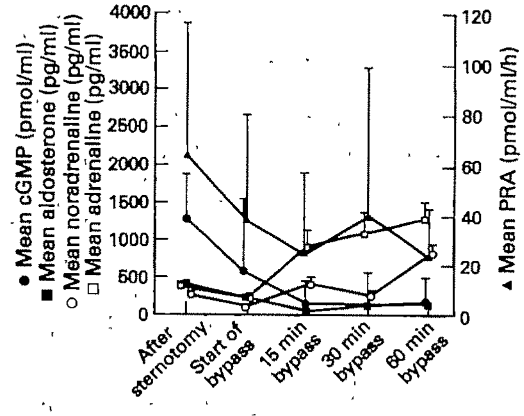


Figure 2 Changes in mean values of plasma renin activity (PRA) and aldosterone, adrenaline, noradrenaline, and urinary cGMP concentrations with time during bypass

the least squares method. A p value of $<0{\cdot}05$ was regarded as statistically significant.

Results

CARDIOPULMONARY BYPASS

Figures 1 and 2 show changes in mean plasma concentrations of ANP, arginine vasopressin, aldosterone, adrenaline, and noradrenaline, and plasma renin activity. Mean concentrations of urinary cGMP are also shown. Results are given up to one hour of bypass although only two patients continued to require bypass for that period. Plasma ANP decreased during bypass and increased significantly ($p < 0{\cdot}05$; fig 3) when bypass stopped. Urinary cGMP decreased significantly ($p < 0{\cdot}05$) during bypass, reflecting the changes in ANP. Central venous pressure declined and then increased as atrial emptying and filling occurred. Plasma arginine vasopressin, adrenaline, and noradrenaline increased during bypass where aldosterone concentration and plasma renin activity decreased; none of these changes reached statistical significance.

POSTOPERATIVE PERIOD

Figures 3 and 4 show changes at the end of bypass and during the subsequent 24 hours in the values already discussed. The significant increase in plasma ANP and urinary cGMP after the end of bypass lagged behind the increase in mean central venous pressure. Aldosterone concentration and plasma renin activity increased and arginine vasopressin decreased after bypass but these changes were not significant. Over the next 24 hours ANP concentration declined significantly ($p < 0{\cdot}05$), to a trough at 22 hours, then increased at 24 hours.

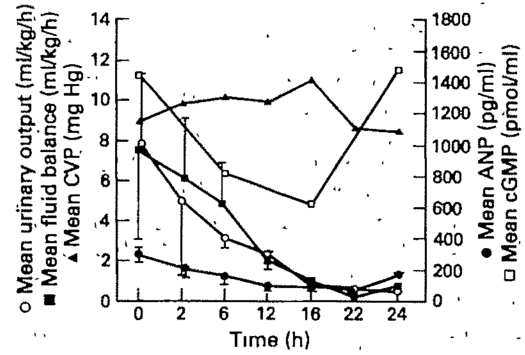


Figure 3 Changes in means for plasma renin activity (PRA) and aldosterone and arginine vasopressin (AVP) concentration with time after operation.

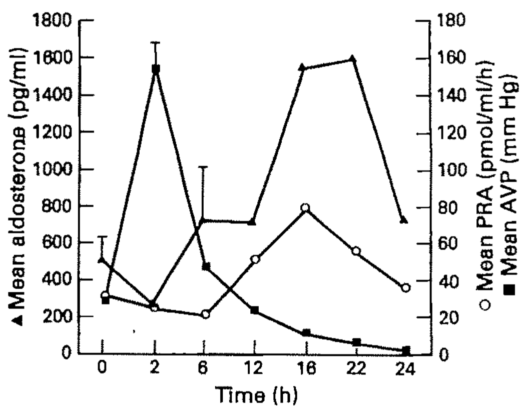


Figure 4 Changes in means for ANP concentration mean cumulative fluid balance, mean urinary output, central venous pressure (CVP), and urinary cGMP concentration with time after operation.

The changes in plasma ANP correlated significantly with mean fluid balance ($r = 0{\cdot}96$, $p < 0{\cdot}001$; fig 5), but not with mean central venous pressure ($r = 0{\cdot}2$, $p = 0{\cdot}6$). Plasma aldosterone and plasma renin activity increased during the postoperative period. Aldosterone concentrations peaked significantly ($p < 0{\cdot}05$) at 22 hours in relation to that immediately after bypass and plasma renin activity peaked at 16 hours. Arginine vasopressin concentration significantly decreased ($p < 0{\cdot}05$) to a trough at 24 hours after peaking two hours after the end of bypass. Mean cGMP also declined in the postoperative period but increased again at 24 hours, although none of these changes were significant. Mean central venous pressure did not change significantly in the postoperative period. Mean adrenaline and noradrenaline were measured less frequently after operation because of the increased volume of plasma required for the assay. The six hour postoperative mean concentration of adrenaline was 1633 (208) pg/ml and noradrenaline 610 (169) pg/ml, whereas the corresponding 24 hour concentrations were 838 (123) pg/ml and 367 (180) pg/ml. After operation only ANP had a significant correlation with urinary output ($r = 0{\cdot}97$, $p < 0{\cdot}001$; fig 6). Arginine vasopressin ($r = 0{\cdot}6$, $p = 0{\cdot}1$) and cGMP ($r = 0{\cdot}5$, $p = 0{\cdot}5$) concentrations had non-significant positive correlations and aldosterone concen-

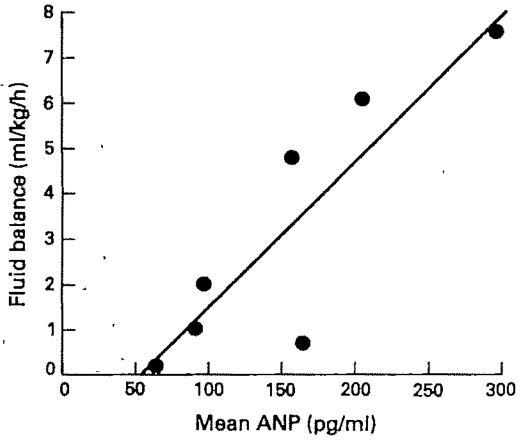


Figure 5 Correlation between mean plasma ANP concentration and mean cumulative fluid balance.

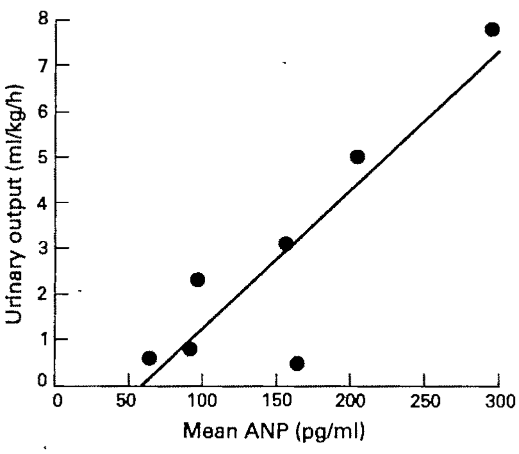


Figure 6 Correlation between mean plasma ANP concentration and mean urinary output.

tration ($r = -0\cdot 5$, $p = 0\cdot 1$) and plasma renin activity ($r = -0\cdot 5$, $p = 0\cdot 2$) non-significant negative correlations with urinary output. Similarly, there were non-significant negative correlations between ANP and plasma renin activity ($r = -0\cdot 6$, $p = 0\cdot 02$) and aldosterone ($r = -0\cdot 7$, $p = 0\cdot 1$) and non-significant positive correlations between ANP and cGMP ($r = 0\cdot 5$, $p = 0\cdot 2$) and arginine vasopressin ($r = 0\cdot 6$, $p = 0\cdot 2$).

Discussion

We have shown the different pattern of release of water balance hormones in response to cardiopulmonary bypass in children. Changes in plasma ANP are of interest in that the pattern is consistent and thus predictable. During cardiopulmonary bypass concentrations decreased as the atria were emptied and significantly increased as the heart was filled at the end of bypass, as would be expected if ANP is secreted by atrial myocytes in response to local wall stretch.[7] Wall stretch is produced by increasing intravascular volume and thus the physiological release mechanism for ANP was shown by the strong correlation between ANP and mean fluid balance in the postoperative period. The narrow band of change in central venous pressure probably explains the far better correlation between ANP and mean fluid balance.

The decline in plasma ANP was shown to be a function of decreasing intravascular volume therefore confirming that the decline in ANP is only rarely related to atypical tamponade.[13 14] Furthermore, the pattern of ANP release seems predictable despite known variations according to the intracardiac repair.[15 16]

The postoperative rise in aldosterone and renin may be explained by the inhibitory effect on their release by ANP,[17] although it may also be explained by the fluid restriction in the postoperative period. The peaks in arginine vasopressin concentration coincided with declines in ANP. This may be predicted as ANP also inhibits arginine vasopressin release.[18] Overall, however, arginine vasopressin tended to decrease after operation and had a weak positive correlation with ANP. Changes in urinary cGMP reflected changes in plasma ANP, as would be expected if it is the second messenger for ANP.[19] As with all other hormones measured the correlation with ANP did not reach statistical significance.

Although positive (arginine vasopressin and cGMP) and negative (plasma renin and aldosterone) relation with urine output were documented none reached statistical significance. The only hormone that had a positive correlation with urinary output was ANP ($r = 0\cdot 97$, $p < 0\cdot 001$). This illustrates its known diuretic action.[20]

Our results show a pattern of change in water balance hormones after cardiopulmonary bypass in children and provide a useful framework for therapeutic intervention that with the use of angiotensin converting enzyme inhibitors and possibly intravenous ANP[21] is increasingly targeted at the endocrine system.

This work was supported by the British Heart Foundation

1 Chiu RCJ, Samjon R Complement (c3, c4) consumption in cardiopulmonary bypass, cardioplegia and protamine administration *Ann Thorac Surg* 1984;37·229–32
2 Fagmoville ME, Deby-Dupont G, Larbuisson R, *et al* Prostaglandin E2, prostacycline and thromboxane changes during nonpulsatile cardiopulmonary bypass in humans. *J Thorac Cardiovasc Surg* 1986;91 858–66.
3 Hine IP, Wood WG, Mainwaring-Burton RW, *et al* The adrenergic response to surgery involving cardiopulmonary bypass as measured by plasma and urinary catecholamine concentrations. *Br J Anaesth* 1976;48.355–63.
4 Milne EMG, Elliot MJ, Pearson DT, Holden MP, Alberti KGMM The effect on intermediary metabolism of open heart surgery with deep hypothermia and circulating arrest in infants of less than 10 kg body weight. A preliminary study *Perfusion* 1986,1·29–40
5 Baum D, Dillard DH, Porter D Inhibition of insulin release in infants undergoing deep hypothermic cardiovascular surgery *N Engl J Med* 1968,279.1309–14
6 Baum D, Dillard DH, Mohri H, Crawford EW. Metabolic aspects of deep surgical hypothermia in infancy *Pediatrics* 1968;42 93–105
7 Brenner BM, Ballermann BJ, Gunning ME, Zeidel ML Diverse biological actions of atrial natriuretic peptide. *Physiol Rev* 1990;70.665–99.
8 Burch M, Till JA, Rigby ML, *et al*. Plasma concentration of atrial natriuretic peptide in spontaneous atrioventricular re-entrant tachycardia of childhood *Br Heart J* 1990, 64.317–20.
9 Dewar ML, Walsh G, Chiu CJ, *et al*. Atrial natriuretic factor· response to cardiac operation *J Thorac Cardiovasc Surg* 1988,96:266–70.
10 Asari H, Kondo H, Ishihara A, Ando K, Marumo F. Extra corporeal circulation influence on plasma atrial natriuretic peptide concentration in cardiac surgery patients *Chest* 1989,96 757–60.
11 Oyama T, Kudo T, Kudo M, *et al* Plasma concentration of human atrial natriuretic polypeptide during cardiopulmonary bypass under fentanyl anaesthesia. *Agressologie* 1986;27 687–9
12 McIntosh N, Smith A Serial measurement of arginine vasopressin in the newborn *Arch Dis Child* 1985,60 1031–5.
13 Shore DF, Capuani A, Lincoln C Atypical tamponade after cardial operation in infants and children *J Thorac Cardiovasc Surg* 1982;83 449–52
14 Burch M, Lincoln C, Carter N, Smith A Acute sternal opening after cardiac surgery in children· effect on plasma atrial natriuretic peptide. *J Cardiovasc Surg* 1991;32: 246–50.
15 Stewart JM, Seligman KP, Zeballos G, *et al* Elevated atrial natriuretic peptide after the Fontan procedure *Circulation* 1987;76:77–8
16 Burch M, Shineborne EA, Rigby ML, *et al* Plasma atrial natriuretic peptide after the Fontan procedure and total cavopulmonary connection *Int J Cardiol* 1990,27·161–5
17 Maack T, Marion DN, Camargo MJ, *et al*. Effects of auriculin on blood pressure, renal function and the renin-aldosterone system in dogs. *Am J Med* 1984,77:1069–75
18 Samson WK. Atrial natriuretic factor inhibits dehydration and haemorrhage induced vasopressin release *Neuroendocrinology* 1985;40 277–9.
19 Hamlet P, Tremblay J, Pang SC, *et al*. Effect of native and synthetic atrial natriuretic factor on cyclic GMP *Biochem Biophys Res Commun* 1984;123:515–27
20 Anderson JV, Donckier J, Payne NN, Beacham JD, Bloom SR. Atrial natriuretic peptide: evidence of action as a natriuretic hormone at physiological plasma concentrations in man. *Clin Sci* 1987,72 305–12.
21 Saito Y, Nakao K, Nishimura A, *et al* Clinical application of atrial natriuretic polypeptide in patients with congestive heart failure: beneficial effects on left ventricular function *Circulation* 1987;76·115–24

Br Heart J 1992;68:313–9

Magnetic resonance imaging of hearts with atrioventricular valve atresia or double inlet ventricle

I C Huggon, E J Baker, M N Maisey, A P Kakadekar, P Graves, S A Qureshi, M Tynan

Abstract

***Objective*—To investigate the effectiveness and limitations of magnetic resonance imaging in defining cardiac anatomy in patients with double inlet ventricle or atrioventricular valve atresia.**

***Design*—Magnetic resonance images were reviewed retrospectively without reference to other morphological data.**

***Setting*—A tertiary referral centre for paediatric cardiology.**

***Patients*—18 patients (aged 8 days to 27 years) with a suspected univentricular atrioventricular connection.**

***Methods*—Imaging by a 1·5 T whole body magnetic resonance system with imaging planes adjusted to individual patient anatomy to best define the cardiac morphology. A complete sequential diagnosis obtained from an independent interpretation of the images was compared with the diagnosis obtained from cross sectional echocardiography and angiocardiography.**

***Results* There was substantial accord between the diagnosis from magnetic resonance alone and that from other methods. In the six instances where there was not accord the magnetic resonance diagnosis was considered to be correct in two cases and incorrect in three cases. In the remaining case no consensus could be reached. In eight patients magnetic resonance imaging provided anatomical information additional to that from other methods. The strengths of magnetic resonance were in imaging the pulmonary arteries and their abnormalities and identifying juxtaposed atrial appendages but there were some deficiencies in identifying Blalock-Taussig shunts.**

***Conclusion*—Magnetic resonance imaging provided detailed information about all aspects of cardiac morphology in patients with a suspected diagnosis of univentricular atrioventricular connection. Often it provided additional information to echocardiography. Its use in selected patients should give valuable complementary information.**

(*Br Heart J* 1992;68:313–9)

The optimum management of patients with congenital heart disease depends on obtaining a precise anatomical diagnosis.[1 2] While cross sectional echocardiography remains an important technique for obtaining this anatomical information, magnetic resonance imaging has recently been shown to be an invaluable adjunct in the assessment of congenital malformations of the heart and great vessels.[3-5] In this study we review our experience with magnetic resonance imaging in the diagnosis of congenital cardiac malformations in which there was an abnormality of atrioventricular connection. In each patient a diagnosis of univentricular atrioventricular connection was considered in the initial differential diagnosis, though in some cases the final diagnosis was revised. The diagnoses made by magnetic resonance imaging were compared with those made by echocardiography, and where applicable, by angiocardiography.

Patients and methods

Eighteen patients (aged eight days to 27 years, median 2·5 years) underwent magnetic resonance imaging with a 1·5 T whole body imaging system (Gyroscan, Philips Medical Systems). We sedated the younger children with chloral hydrate (100 mg/kg) or chloral hydrate (75 mg/kg) combined with trimeprazine (2 mg/kg). The scans were gated from the electrocardiogram by means of electrodes placed close to the cardiac apex to reduce flow distortion of the signal. The trigger delay time was 15 ms. All of the patients were in sinus rhythm except one who had complete heart block with a regular ventricular rate of 70/min. A T1 weighted spin-echo sequence was used in all of the patients. Echo times were 20 or 30 ms and the time to repeat was determined by the software based on the patients heart rate and varied between 312 and 500 ms. Generally, four phase encoding steps were used, but where this would have entailed an acquisition time of more than about six minutes only two were used. The field of view ranged from 101 to 450 mm and the final matrix size was 256 by 256. Infants were imaged inside a proton head coil, and a body coil was used for the larger children and young adults. Each patient was first scanned in a coronal plane in a non-gated mode and the resulting images were then used to plan the plane of subsequent scans. Magnetic resonance imaging allows scanning in any plane and the simultaneous acquisition of several

Department of Paediatric Cardiology, Guy's Hospital, London
I C Huggon
E J Baker
A P Kakadekar
S A Qureshi
M Tynan

Department of Radiological Sciences, Guy's Hospital, London
M N Maisey
P Graves

Correspondence to:
Dr I C Huggon, Department of Paediatric Cardiology, 11th Floor, Guy's Tower, Guy's Hospital, St Thomas's Street, London SE1 9RT

Accepted for publication 5 March 1992

parallel image slices within that plane. Angles and offsets of the individual imaging planes were selected for each patient by a cardiologist present at the investigation, in the light of previously acquired images and knowledge of the anatomy already established including the results of previous echocardiography. The planes were chosen first to image areas of the anatomy about which there was most uncertainty, other areas being imaged as time allowed. The slice thickness ranged from 5 mm to 10 mm and was chosen according to the size of the patient. Thinner slices can resolve smaller structural details than thicker slices but are associated with a higher signal to noise ratio and deterioration in image quality. The number of slices in a particular plane was chosen to include all areas of interest.

We studied patients with an abnormality of atrioventricular connection in whom a diagnosis of a univentricular atrioventricular connection was considered in the initial differential diagnosis. Limited access to MR imaging sessions meant that only about half the patients eligible for inclusion in the series during the period of the study could be scanned. Patients in whom more complete definition of the complex cardiac anatomy was required were selected for magnetic resonance imaging. In several patients, determination of the anatomy of the pulmonary arteries was the main object of the scan and defining the intracardiac anatomy was a secondary consideration. No patient had had definitive surgery before scanning but 11 had previously had one systemic to pulmonary shunt and two patients had had two shunts. Two patients had had pulmonary artery banding, one an atrial septectomy, and one repair of coarctation. All patients had clinical evaluation and cross sectional and Doppler echocardiography. Angiocardiography was performed when clinically indicated.

Table 1 Sequential segmental diagnosis from magnetic resonance imaging

Patient number	*Atrioventricular connection*	*Ventriculoarterial connection*	*Comments*
1	DIRV	Double outlet right ventricle	Common atrioventricular valve
2	Absent right	Discordant	Double inlet left ventricle on echocardiography
3	Absent right	Double outlet right ventricle	Hypoplastic right atrioventricular valve and concordant atrioventricular connection
4	DILV	Discordant	
5	Absent right	Concordant	Pulmonary atresia
6	DILV	Discordant	Right ventricle to the left of left ventricle
7	DILV	Discordant	
8	DILV	Double outlet right ventricle	Juxtaposed atrial appendages
9	Absent right	Concordant	
10	Concordant	Concordant	Juxtaposed atrial appendages, imperforate right atrioventricular valve
11	Absent right	Concordant	Pulmonary atresia
12	Concordant	Double outlet right ventricle	Imperforate left atrioventricular valve
13	DILV	Concordant	Common atrioventricular valve
14	Absent right	Concordant	
15	DILV	Single outlet right ventricle	Pulmonary atresia
16	Absent right	Concordant	
17	DIRV	Concordant	Double inlet left ventricle on angiogram
18	Concordant	Concordant	Pulmonary atresia, imperforate right atrioventricular valve

DIRV, double inlet left ventricle; DILV, double inlet left ventricle.

INTERPRETATION OF THE MAGNETIC RESONANCE SCANS

The images were acquired with the help of any available diagnostic information on the patient. For the purposes of this study, however, they were reviewed without reference to any previous information available on the patients. Each scan was reported according to the following protocol. First the technical details of the scan acquisition were noted. Then the cardiac morphology was analysed by the sequential approach and the associated anomalies were recorded as follows.

Venous connections

Systemic and pulmonary veins were identified on the images and each followed to its draining atrium, which was then identified as described below.

Atrial anatomy

The atrial arrangement was assessed according to the morphology of the atrial appendages, the right atrial appendage being identified by a wide base and triangular shape and the left by a narrow base and tubular shape. The relation of the great vessels at the level of the diaphragm and the anatomy of the bronchi were recorded where available. Defects within the atrial septum were noted.

Atrioventricular connection

The atrioventricular connection was determined by identifying the number of atrioventricular valves present and the morphology of the atria and the ventricles that they connected. Where a ventricular cavity was separated by tissue from an atrial cavity, the intervening tissue was identified either as an extension of bright fatty sulcal tissue, indicating an absent connection, or as an imperforate valve.

Ventricular anatomy

The ventricular morphology was identified primarily by the trabecular pattern. In cases of uncertainty the shape of the ventricles, their relative positions, and the number and the insertion of the papillary muscles were considered. The site and size of any ventricular septal defects were noted.

Ventriculoarterial connection

The pulmonary artery and aorta were identified by their location and branching patterns and traced back to the ventricle of origin by following their course through several image slices if necessary. The presence of a complete muscular infundibulum and of stenosis or atresia were documented.

The great arteries

The relation of the aorta and the pulmonary artery at the valve level were established. The course of the aortic arch was followed for any abnormality. The pulmonary artery and its main branches were identified in transverse and oblique sagittal or coronal images. The size of the arteries and any stenosis were recorded. Aorto-pulmonary shunts, when present, were identified on these images.

Table 2 Additional information from magnetic resonance imaging

Patient number	*Additional information obtained*
4	Pulmonary artery anatomy shown more clearly than on angiography
5	Left pulmonary artery stenosis associated with left Blalock shunt
8	Juxtaposed atrial appendanges
9	Stenosis of the left pulmonary artery
10	Juxtaposed atrial appendanges
11	Absent left pulmonary artery
14	Pulmonary artery anatomy demonstrated (no angiogram performed)
15	Absence of substantial central pulmonary arteries (later confirmed by angiogram)

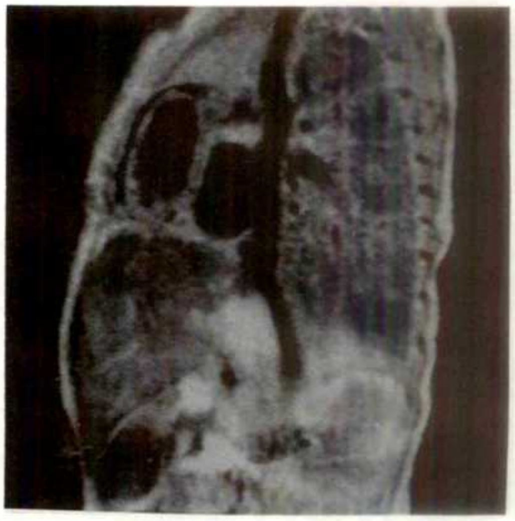


Figure 1 A sagittal slice from the scan of patient 13 showing the connection of inferior and superior caval veins to the right atrium.

The images were reviewed by considering each set of slices together and following structures identified in one slice through the adjacent slices in order to appreciate fully the relation and connections.

Subsequently the results of this assessment of the magnetic resonance diagnosis were compared with the diagnoses made by echocardiography and angiocardiography. Where the diagnoses from magnetic resonance imaging and from other techniques did not accord the information from the magnetic resonance imaging, echocardiography, and angiocardiography was reviewed together by two of the authors to arrive at a consensus diagnosis. Necropsy results were reviewed where available.

Results

Scans of diagnostic quality were obtained in all the patients. Table 1 summarises the findings in individual patients. There was considerable motion artefact in four of the studies but this did not affect interpretation of the scans.

In 12 of 18 patients there was no substantial discord between the initial interpretation of the magnetic resonance scan and the information available from cross sectional echocardiography and angiocardiography. In six of 18 cases there was substantial discord. In eight of 18 patients the magnetic resonance scan provided additional anatomical information not available from the other techniques (table 2). In those patients in whom examinations did not accord a consensus diagnosis reached after consideration of all the available information indicated that the magnetic resonance diagnosis was misleading in three patients but correct in two. In the remaining patient a consensus could not be reached because the angiographic and magnetic resonance findings were contradictory (table 3).

Postmortem pathology was available in only one of the patients (patient 13, table 1) and this confirmed correct interpretation of the magnetic resonance scan.

VENOUS CONNECTIONS

In 17 of the 18 patients the drainage of the superior and inferior caval veins into the right atrium (fig 1) and of the pulmonary veins into the left atrium (fig 2) was clearly shown. Scans of the remaining patient showed the inferior caval vein draining to the right atrium but the superior caval veins and pulmonary veins were not seen completely. A left-sided superior caval vein known to be present from echocardiography in one patient was not noted on the

Table 3 Lack of accord between magnetic resonance imaging and other techniques

Patient number	*Diagnosis from magnetic resonance*	*Diagnosis from other techniques*	*Conclusion from consensus diagnosis*
2	Absent right AV connection	Double inlet left ventricle	Magnetic resonance misinterpreted
3	Absent right AV connection	Hypoplastic right AV valve	Magnetic resonance misinterpreted
3	Right atrial isomerism	Usual atrial arrangement	Magnetic resonance misinterpreted
8	Double outlet right ventricle	Double outlet left ventricle	Magnetic resonance correct
12	Imperforate left AV valve	Absent left AV connection	Magnetic resonance correct
17	Double inlet right ventricle concordant VA connection	Double inlet left ventricle discordant VA connection	Undecided

AV connection, atrioventricular connection; VA connection, ventriculoarterial connection.

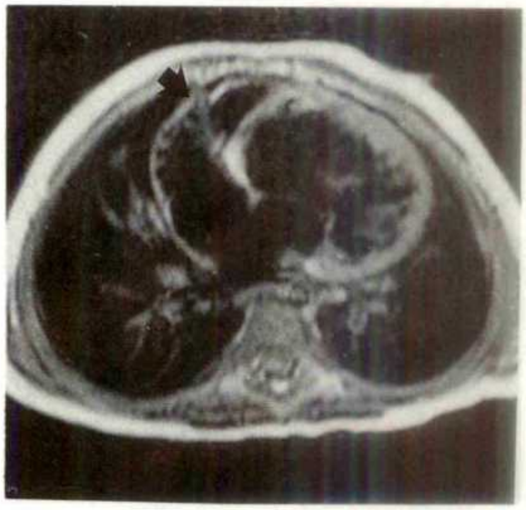


Figure 2 Drainage of pulmonary veins into the left atrium in patient 16. Right atrial appendage (indicated by the arrow), a large atrial septal defect, and dominant left ventricle are also shown.

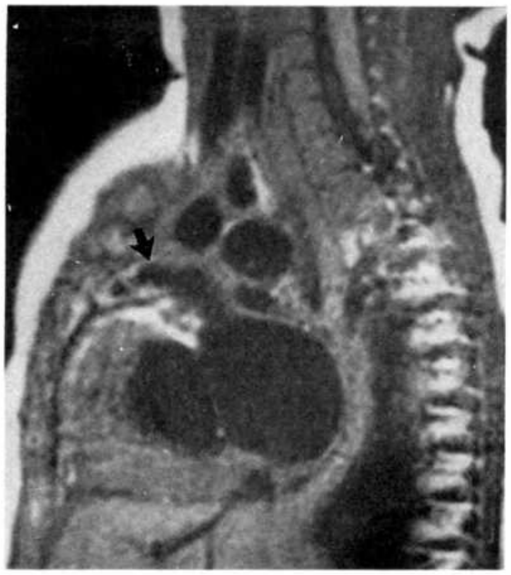


Figure 3 Morphologically left atrial appendage, indicated by the arrow, shown connecting to the dilated left atrium of patient 14.

magnetic resonance images on the first interpretation but was identified on further review of the images.

ATRIAL ANATOMY

In all of the patients the relation of the aorta and the inferior caval vein at the diaphragm could be clearly demonstrated on transverse, coronal, or serial sagittal views.

In 11 of the 18 patients, both the atrial appendages could be identified as either morphologically right or left (figs 2 and 3). In a further six patients a morphologically right atrial appendage was shown on the right side but the left sided atrial appendage was not clearly shown. In one patient neither atrial appendage was adequately imaged. Of the 11 patients in whom both atrial appendages were identified one was initially considered to have right isomerism of the atrial appendages on the basis of the magnetic resonance scan alone but the diagnosis was revised to the usual arrangement when all the information was considered. The remaining 10 all had usual atrial arrangement. Two of the patients with the usual atrial arrangement had unsuspected juxtaposition of the atrial appendages. In one of these patients, surgical confirmation was available and in the second the magnetic resonance images provided the only evidence of juxtaposition.

The relative sizes of the atria were well seen in all of the patients. In seven a large atrial septal defect was shown but in the remainder it was not possible to confirm or exclude a defect. Because of its thinness relative to the thickness of the image slices, the atrial septum is subject to "dropout" on magnetic resonance images that is analogous to that seen with cross sectional echocardiography.

ATRIOVENTRICULAR CONNECTION

Magnetic resonance imaging showed the atrioventricular connection in all 18 patients. In 16 of these the initial interpretation of the images was correct whereas in two it was incorrect (one with a double inlet left ventricle and one with a hypoplastic right atrioventricular valve with concordant connection).

Of the 16 patients eight had double inlet ventricle, five had absent right-sided connection (fig 4), and three had concordant connection, but with an imperforate right-sided atrioventricular valve in two and an imperforate left sided atrioventricular valve in one (fig 5). The latter patient (patient 12, table 3) had been considered to have an absent left atrioventricular connection on echocardiography but was confirmed to have an imperforate valve after review of all the diagnostic information.

In six of the seven patients with double inlet left ventricles, the atrioventricular connections were correctly identified; the seventh was initially misinterpreted as an absent right connection on the magnetic resonance images (patient 2, table 3). Two patients had double inlet right ventricle diagnosed on magnetic resonance imaging. The diagnosis in one of these was confirmed by the other techniques but no consensus was reached about patient 17 because the angiograms seem to suggest a diagnosis of double inlet left ventricle.

In one patient the anatomy by magnetic resonance was thought to be that of absent right connection but on review the echocardiographic diagnosis of hypoplastic right atrioventricular valve was correct and the magnetic resonance images had been misinterpreted.

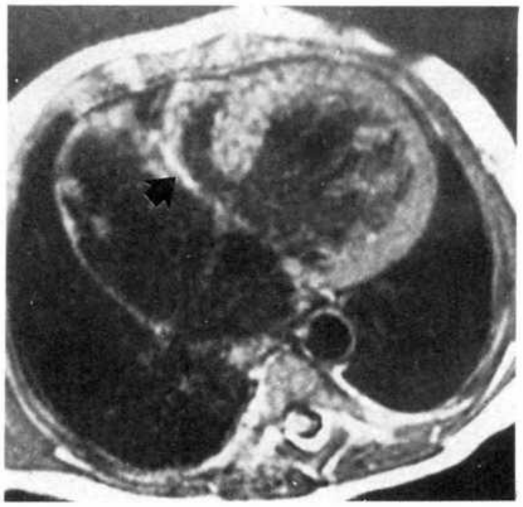


Figure 4 Absent right connection. Sulcal fat can be seen as a bright line (arrow) separating the right atrium from the small right ventricle. Right atrial appendage is also shown and the morphological left ventricle can be distinguished from the smaller morphological right ventricle (patient 14).

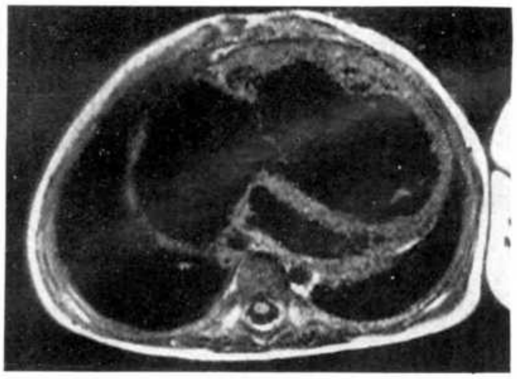


Figure 5 Imperforate left atrioventricular valve (patient 12). Note the absence of penetration of sulcal fat to the crux of the heart (arrow) in contrast to the absent right connection in fig 4.

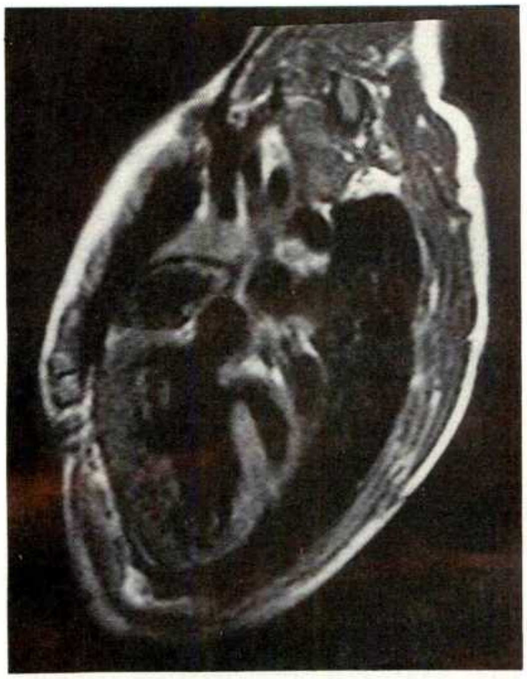


Figure 6 Oblique sagittal view of patient 17 showing a small smooth-walled left ventricle posteriorly and trabeculated right ventricle anteriorly. The angiogram was more suggestive of double inlet left ventricle than the double inlet right ventricle indicated by the magnetic resonance images. Right and left atrial appendages and a ventricular septal defect are also shown.

VENTRICULAR MORPHOLOGY

The ventricular morphology of one or both the ventricles could be determined by magnetic resonance in all patients. In 16 of the patients we determined the morphology by the trabecular pattern and in two by taking other features into account.

In eight patients the characteristic trabecular pattern could be identified in both the ventricles (figs 4 and 6), though in one of these patients (patient 17, table 3), with a double inlet connection, the angiographic and magnetic resonance findings were conflicting. In a further eight patients only the left ventricular trabeculations were identified, the right ventricle being very small. In the remaining two patients the trabecular pattern was not identified with certainty, but the ventricular morphology was inferred from the shape and the relative positions of the ventricles.

The predominance of patients with univentricular atrioventricular connection made the use of papillary muscle numbers and site of insertion as an indication of ventricular morphology inapplicable in most cases. In only five of the 18 patients were two distinct papillary muscles seen in the left ventricle and the septal attachments of the tricuspid valve tensor apparatus were seen in only three patients.

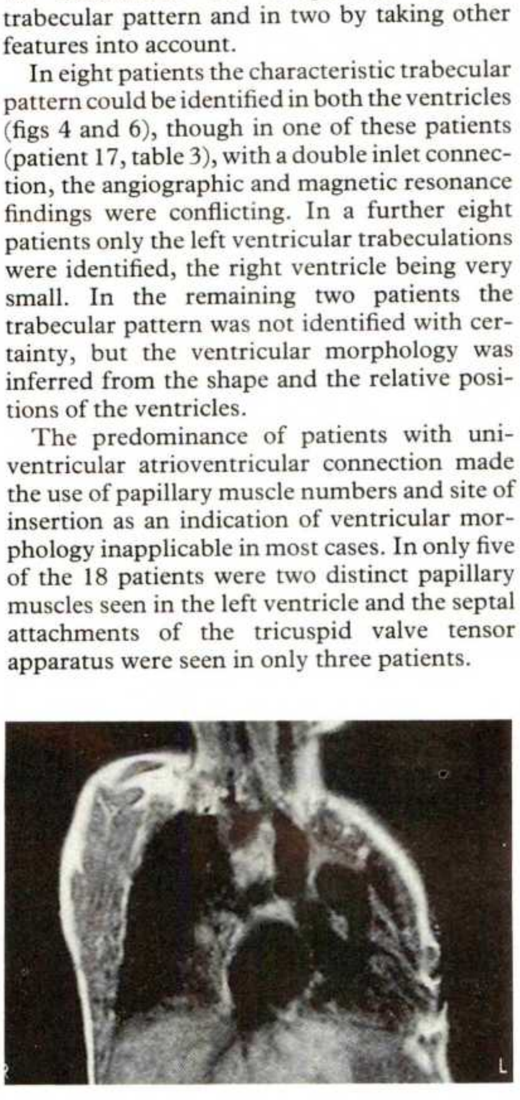


Figure 7 Double outlet from the right ventricle in patient 1. Posterior great artery can be clearly identified as an aorta by its continuity with a carotid artery. This patient also has a double inlet to the right ventricle with a common atrioventricular valve.

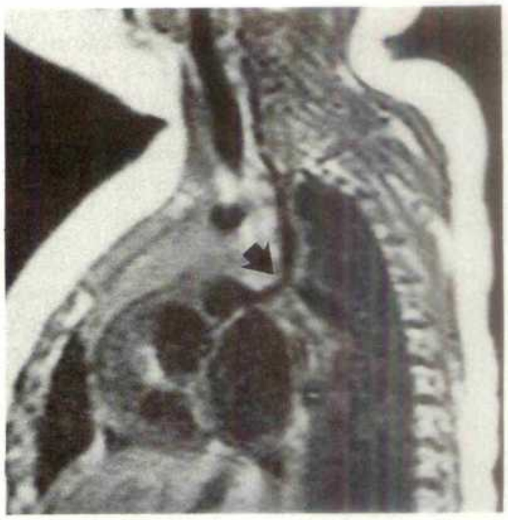


Figure 8 Left pulmonary artery in patient 3 can be seen to be distorted and stenosed at the site of a patent Blalock-Taussig shunt.

RELATIVE POSITIONS OF THE VENTRICLES

The right ventricle was anterior and/or superior to the left ventricle in 17. In the remaining patient, with dextrocardia and double inlet left ventricle, the right ventricle was directly to the left of the morphologically left ventricle (patient 6).

VENTRICULAR SEPTAL DEFECTS

The site and size of a ventricular septal defect was determined in 14 patients but the rims of the defect were not sufficiently well defined to determine the size or position of a defect in the remaining three where a defect was known to be present.

VENTRICULOARTERIAL CONNECTION

In all of the patients the type of the ventriculoarterial connection was correctly determined (table 1). Nine patients had a concordant ventriculoarterial connection, four had a discordant connection, four had a double outlet right ventricle and one had a single outlet aorta arising from the right ventricle. Figure 7 shows the double outlet right ventricle in patient 1. In one patient (patient 8) the echocardiogram suggested double outlet left ventricle, but the magnetic resonance imaging showed double outlet right ventricle, which was the correct diagnosis on review.

The infundibular morphology was well demonstrated in all the patients. Four patients had a bilateral complete muscular infundibulum, of whom two had a double outlet right ventricle and one had a concordant and one a discordant ventriculoarterial connection. All of the three patients with only a subaortic infundibulum had discordant ventriculoarterial connection. A complete subpulmonary infundibulum was identified in the remaining 11 patients.

GREAT ARTERIES

The relation of the great arteries at the level of their valves was defined in all patients except one, in whom the main pulmonary artery was entirely absent. The aorta was posterior and to the right of the pulmonary artery in seven patients, anterior and to the left in four, anterior and to the right in three, and directly anterior in three.

AORTIC ARCH

The aortic arch was right sided in four patients (three with discordant and one with concordant ventriculoarterial connection) and left sided in the remaining 14. In 11 patients the arch was widely patent throughout its course. In one patient the aortic wall was irregular because of a previous coarctation repair but the aortic lumen was adequate. In the remaining six patients views of the complete arch were not obtained.

AORTOPULMONARY SHUNTS

Thirteen patients had shunts, in two cases bilaterally. A right Blalock-Taussig shunt was seen on the scans of three patients, a left Blalock-Taussig shunt in six, and none in nine (fig 8). On a further review of the scans when the information about the presence of shunts was available to the observer, three of the six shunts missed on the first review could be identified: the remaining three shunts had not been imaged.

PULMONARY ARTERIES

In 14 patients the pulmonary arteries were seen well enough to assess their size and in four patients one or both pulmonary arteries were not visualised. In two of these four patients, the pulmonary artery was absent on angiography. In the remaining two the failure to identify the pulmonary arteries was attributed to the optimum image planes not being selected.

Discrete stenosis was shown in the left pulmonary artery in four patients and in the right pulmonary artery in two (fig 8). In one patient the main pulmonary artery was absent and in two the site of a pulmonary artery band was seen. It was generally possible to image the right and left pulmonary arteries as far as the division of the major branches, the limiting factor being respiratory movement that blurred the image distally.

Discussion

Magnetic resonance imaging is a safe, non-invasive method of obtaining anatomical information in congenital heart disease and is applicable to all ages. It was shown to be of value initially in patients with coarctation of the aorta and ventricular septal defect[3 5 6] and subsequently in patients with atrioventricular septal defect[7] and patients with double outlet right ventricle.[8] In this study we investigated the role of magnetic resonance imaging in patients with suspected univentricular atrioventricular connection. Our aim was not only to study the atrioventricular connection itself, but also to study the associated features that contribute to a full anatomical description and which may influence the subsequent clinical management.

We showed that high resolution images can be obtained in patients with a wide range of age and build and we successfully and satisfactorily demonstrated their complex anatomy. To achieve this we avoided restricting ourselves to the use of fixed orthogonal planes, with which others have reported limited success.[4 5] The major advantages of magnetic resonance imaging over both cross sectional echocardiography and angiocardiography are that any plane or series of planes of the heart can be imaged, irrespective of the nature and depth of the interposed tissues such as fat and lung, thus providing an unlimited "window" of access.

We planned each set of imaging planes separately, bearing in mind the anatomy already established for the patient, the position of the recognised landmarks on the images already obtained, and the aspects of the anatomy that required clarification. Optimum imaging sometimes required scanning planes that were oblique or double oblique with respect to the orthogonal planes. Thus during the scanning, the presence of a paediatric cardiologist with a thorough knowledge of the three dimensional anatomy of the heart was essential to plan the subsequent imaging planes. At the outset, it was important to concentrate on obtaining the appropriate images to clarify the anatomical issues in question. For example, to obtain satisfactory views of both the pulmonary arteries, transverse images that included the pulmonary artery bifurcation were followed up by oblique sagittal or coronal scans planned parallel to the right and left pulmonary arteries based on the transverse images obtained. However, usually a review of the images after a scan had been completed showed considerable additional information on the anatomy that had not specifically been sought. Furthermore, in several instances the magnetic resonance images provided information additional to that available from angiocardiography and cross sectional echocardiography alone (table 2). For example, the atrial morphological arrangement could often be determined directly from the scans rather than from potentially unreliable inference from the visceral or bronchial arrangement.[9] However, particular care was required in interpretation, because in one case a left atrial appendage was mistakenly identified as a right one because of its oblique plane of section in the image. Juxtaposition of the atrial appendages was shown in two patients in whom this anomaly had not previously been suspected by echocardiography or angiocardiography. Such information could have been obtained angiographically, but only by using extra contrast injections and increasing the fluoroscopy time.

Failure of magnetic resonance imaging to demonstrate the anatomy correctly was attributable to inadequate views and/or misinterpretation of the scans. For instance, Blalock-Taussig shunts present on the images were not always recognised on the first interpretation. In other cases in which an absent right atrioventricular connection was diagnosed in error instead of double inlet left ventricle and hypoplastic right atrioventricular valve respectively, the magnetic resonance images were misinterpreted. It is important to distinguish between an absent right atrioventricular connection, characterised by bright sulcal fat separating the right atrium from the ventricle and the normal connection in which the image slice may have cut across the atrial and ventricular walls tangentially.[10 11] Only by careful examination of all the slices to confirm that the sulcal fat extends through to the crux of the heart can this potential misinterpretation be avoided. The other source of failure to demonstrate structures adequately is the failure to obtain the image planes appropriate for the anatomical feature at issue. With the possible exception of very thin structures, such as the atrial septum, almost any cardiac structure can be satisfactorily imaged by magnetic resonance but in some cases specific and carefully planned imaging planes will be required to achieve this. Therefore a priority of the structures to be imaged should be decided upon before the scan starts so that more important information can be acquired first and less important information later.

Unlike angiocardiography, magnetic resonance imaging is non-invasive and does not use ionising radiation or contrast media. Furthermore, imaging of some structures such as pulmonary arteries by magnetic resonance can be superior to angiography, especially when the optimum site for contrast injection is not accessible to catheterisation. In contrast to echocardiography, magnetic resonance imaging produces a series of related tomographic slice images that include structures such as the spine and trachea, which act as reference points. Therefore, it is easier to appreciate the spatial relation of the heart within the chest and of the chambers and vessels to each other than with cross sectional echocardiography. This is especially true when images acquired previously by a different operator are reviewed. Although currently most magnetic resonance imaging protocols provide only information on structure it is possible to obtain quantitative flow measurements and thus haemodynamic information.[12–14]

Magnetic resonance can produce images of such quality and clarity that it might rightfully be considered the definitive method of structural diagnosis in life. However, it does not replace cross sectional echocardiography: it complements it. The relative low cost, efficacy, and the ease of use of cross sectional echocardiography ensures that it will remain the dominant diagnostic technique in congenital heart disease. The fact that the particular strengths, weaknesses, and limitations of cross sectional echocardiography differ considerably from those of magnetic resonance imaging determines a role for both the techniques. Magnetic resonance imaging should be used in particular in those patients with conditions and aspects of anatomy that cross sectional echocardiography does not image optimally and in patients in whom it will avoid the necessity for invasive investigation.

This research was supported by the British Heart Foundation We acknowledge Sir Philip and Lady Harris, the Special Trustees of Guy's Hospital and Philips Medical Systems for their help in funding this project. Dr J M Parsons and Dr A M Hayes helped in the acquisition of some of the iamges

1 Rigby ML, Carvalho JS, Anderson RH, Reddington A The investigation and diagnosis of tricuspid atresia *Int J Cardiol* 1990,27 1–17.
2 Sade RM, Fyfe DA. Tricuspid atresia Current concepts in diagnosis and treatment *Pediatr Clin North Am* 1990; 37 151–69
3 Parsons JM, Baker EJ, Hayes A, *et al* Magnetic resonance imaging of the great arteries in infants. *Int J Cardiol* 1990,28.73–85.
4 Didier D, Higgins CB, Fisher MR, Osaki L, Silverman NH, Cheitlin MD. Congenital heart disease Gated MR imaging in 72 patients. *Pediatr Radiol* 1986,158 227–35.
5 Baker EJ, Ayton V, Smith MA, *et al* Magnetic resonance imaging of coarctation of the aorta in infants use of high field strength *Br Heart J* 1989,62.97–101.
6 Baker EJ, Ayton V, Smith MA, *et al* Magnetic resonance imaging at a high field strength of ventricular septal defects in infants. *Br Heart J* 1989,62 305–10
7 Parsons JM, Baker EJ, Anderson RH, *et al* Morphological evaluation of atrioventricular septal defects by magnetic resonance imaging *Br Heart J* 1990,64·138–45
8 Parsons JM, Baker EJ, Anderson RH, *et al* Double outlet right ventricle Morphologic demonstration using nuclear magnetic resonance imaging. *J Am Col Cardiol* 1990,18 168–78
9 Caruso G, Becker AE. How to determine atrial situs? Considerations initiated by 3 cases of absent spleen with a discordant anatomy between bronchi and atria *Br Heart J* 1979,41 559–67
10 Jacobstein MD, Fletcher BD, Goldstein S, Riemenschneider TA. Magnetic resonance imaging in patients with hypoplastic right heart syndrome *Am Heart J* 1985, 110 154–8
11 Fletcher BD, Jacobstein MD, Abramowsky CR, Anderson RH. Right atrioventricular valve atresia Anatomic evaluation with MR imaging *Am J Roentgenol* 1986,148 671–4
12 Underwood SR, Firmin DN, Rees RS, Longmore DB Magnetic resonance velocity mapping *Clin Phys Physiol Meas* 1990,11(suppl A)·37–43
13 Rees S, Firmin D, Mohiaddin R, Underwood R, Longmore D. Application of flow measurements by magnetic resonance velocity mapping to congenital heart disease *Am J Cardiol* 1989,64 953–6
14 Moonen CTW, Van Zijl PCM, Frank JA, Le Bihan D, Becker ED Functional magnetic resonance imaging in medicine and physiology *Science* 1990,250 53–61

Br Heart J 1992;**68**:320–2

Successful repair of pulmonary atresia with ventricular septal defect without the use of a conduit: a new surgical option

Report of two cases

Zohair Al-Halees, Omar Galal, Neil Wilson

Abstract

A new technique for the restoration of continuity between the pulmonary artery and the right ventricle in pulmonary atresia with ventricular septal defect without the use of a conduit is described. This was accomplished by anastomosing the inferior margin of the distal pulmonary artery to the apex of a T-shaped infundibular ventriculotomy to form the posterior wall of the reconstructed right ventricular outflow tract. A winged patch of bovine pericardium was then used for the anterior wall to complete reconstruction of the transannular right ventricular outflow tract. This technique was used successfully in two patients.

(*Br Heart J* 1992;**68**:320–2)

The term pulmonary atresia with ventricular septal defect is sometimes used to designate the extreme form of tetralogy of Fallot. The intracardiac anatomy of these patients is similar to that seen in tetralogy of Fallot.[1]

Surgical management has tended to be along the same lines as that of tetralogy of Fallot: the atrial and ventricular defects are closed, all extracardiac sources of pulmonary arterial blood supply excluded, and right ventricle to pulmonary artery continuity restored. This must result in an acceptable peak systolic pressure ratio between the right and left ventricles (usually less than 0·85).[2,3] Generally, a conduit is needed to establish right ventricle to pulmonary artery continuity in pulmonary atresia.

All conduits are liable to progressive stenosis, and valve failure if a valved conduit is used.[3,4] The use of homografts reduces these inherent problems but does not eliminate them.[5] The availability of homografts is a problem in many parts of the world, including Saudi Arabia. Therefore, there are advantages in accomplishing a repair without conduits whenever feasible.

Patients and methods

PATIENT 1

An 11 year old boy with pulmonary atresia and ventricular septal defect was palliated in infancy by bilateral Blalock-Taussig shunts and ligation of multiple aortopulmonary collaterals.

Cardiac catheterisation showed good sized confluent pulmonary arteries, a non-function-

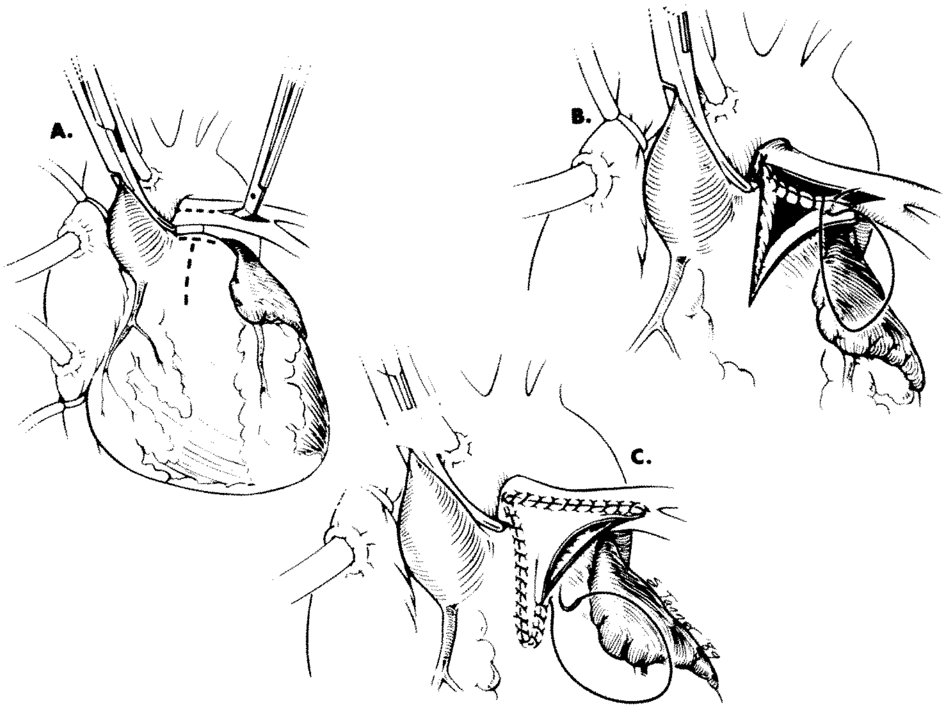


Figure 1 Surgical technique.

Department of Cardiovascular Diseases, King Faisal Specialist Hospital and Research Centre Riyadh, Saudi Arabia
Z Al-Halees
O Galal
N Wilson

Correspondence to
Mr Zohair Al-Halees,
FRCS(C), MBC 16,
King Faisal Specialist
Hospital, PO Box 3354,
Riyadh 11211, Saudi Arabia.

Accepted for publication
29 November 1991.

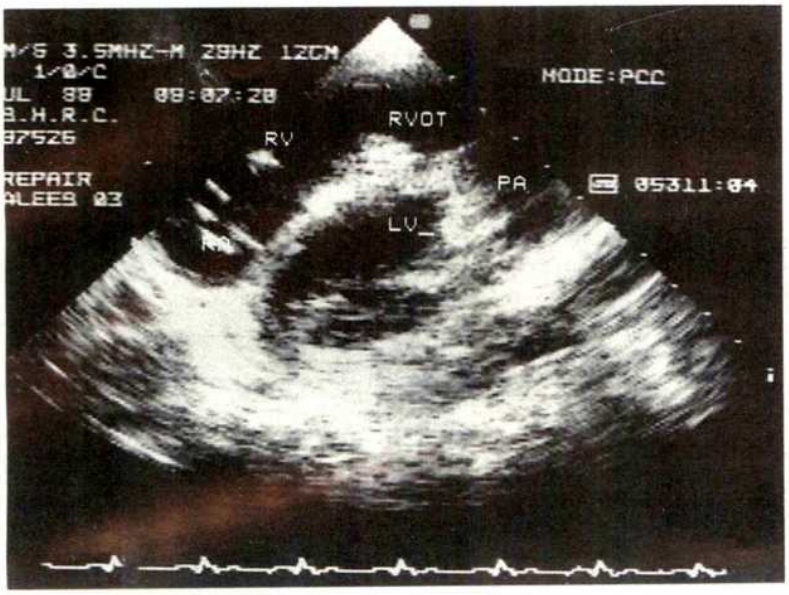


Figure 2 Echocardiogram of the right ventricular outflow tract (RVOT) after repair. Note the widely patent right ventricular outflow tract (RVOT). RV, right ventricle; LV, left ventricle; PA, pulmonary artery.

ing left Blalock-Taussig shunt, and two large aorta to right pulmonary artery collaterals with a functioning right Blalock-Taussig shunt.

At surgery the right Blalock-Taussig shunt and the collaterals were ligated and divided. The ventricular septal defect was closed with a patch of bovine pericardium. Right ventricle to pulmonary artery continuity was established by the technique shown in fig 1.

PATIENT 2

A 3 month old boy presented with cyanosis since the early weeks of life and was found to have pulmonary atresia and ventricular septal defect with a patent ductus arteriosus.

At surgery there was an atretic main pulmonary artery that reached the right ventricle as a fibrous cord. The branch pulmonary arteries were confluent. The patent ductus arteriosus was ligated and the septal defect was closed with a patch of bovine pericardium and right ventricle to pulmonary artery continuity was established by the technique shown in fig 1.

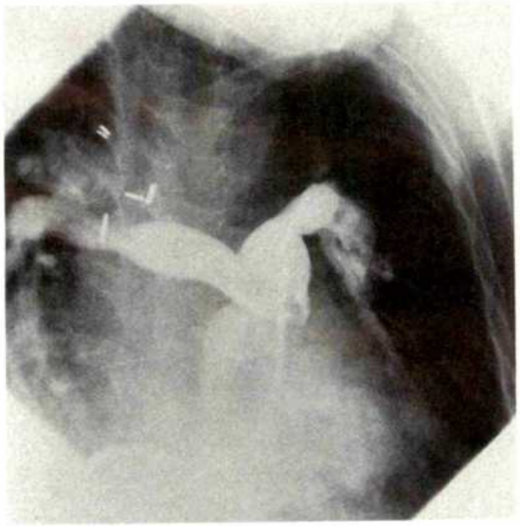


Figure 3 Angiogram of the right ventricular outflow tract pulmonary arteries in patient 1.

Surgical technique

The pulmonary arteries were widely freed to the hila of both lungs to allow good mobility. Any systemic to pulmonary artery shunts were divided and not just ligated. A patent ductus or a ligamentum arteriosum was divided. A T-shaped right ventriculotomy was made in the outflow tract. Through the ventriculotomy, infundibular obstruction was relieved and the ventricular septal defect closed. The confluence of the pulmonary arteries was opened longitudinally (fig 1A). The inferior margin of the pulmonary arteriectomy was pulled down and anastomosed to the apex of the right ventriculotomy to form the posterior wall of the reconstructed right ventricular outflow tract (fig 1B). A wide winged patch of bovine pericardium was used to construct the anterior wall to complete the repair (fig 1C).

Results

Postoperatively there were no specific complications related to the technique in either patient. The right ventricle/left ventricle systolic pressure ratio in both patients before discharge from the intensive care unit was 0·6, as measured on pullback of a pulmonary artery catheter placed at the time of surgery. Before discharge from the hospital echocardiography showed no residual right ventricular outflow tract obstruction or ventricular shunt (fig 2).

On follow up 18 months later both patients were doing well. Patient 2 was symptom free and did not require medical treatment. Patient 1 was in right heart failure and required digoxin, captopril, and diuretics. Because of concern about right heart failure cardiac catheterisation was repeated. This showed a widely patent right ventricular outflow tract without residual gradient (fig 3). There was no residual ventricular septal defect and the right ventricle/left ventricle pressure ratio was 0·6. There was free pulmonary regurgitation. The right ventricular function was mildly impaired.

Discussion

The long-term effects of pulmonary valve insufficiency on right ventricular function after repair of tetralogy of Fallot are still unclear. Experience has established that the right ventricle can function very well without a pulmonary valve for a long period. Unsatisfactory results and late deaths are related to residual right ventricular hypertension rather than pulmonary regurgitation.[6 7]

This picture encouraged us to extend the experience with a transannular patch repair of tetralogy of Fallot to some patients with favourable anatomy who had pulmonary atresia and a ventricular septal defect who otherwise would require a conduit. This same principle of repair was successful in a patient with truncus arteriosus[8] and in anatomical repair of abnormalities of ventriculoarterial connection associated with a ventricular septal defect.[9]

The technique we used to some extent simplifies the surgical total repair of pulmonary atresia with ventricular septal defect. It can be applied in many patients considered for total repair. In some, however, mobilisation of pulmonary arteries is difficult and in addition the gap between the pulmonary artery confluence and the right ventricle is large. For this reason we attempted full mobilisation of the pulmonary arteries to the hila of the lungs and divided collateral arteries and surgically placed shunts or a patent ductus arteriosus. In some cases, however, safe approximation of the pulmonary artery to the right ventricle will not be possible and a conduit will be required. In addition the left anterior descending coronary artery may limit the extent of the T-shaped ventriculotomy. Fortunately we avoided this potential complication, but we think that in many cases a vertical incision could still be manipulated to a horizontal orifice to allow anastomosis with the lower extremity of the pulmonary artery.

Because the postoperative course and the functional state of both patients during 18 months of follow up was acceptable we are reasonably optimistic that the long-term course of these patients may be similar to the long term results of repair tetralogy of Fallot. World wide experience with the repair of tetralogy of Fallot is well known and is generally good.[7,10]

1 Agaraval KC, Edwards WD, Puga FJ, Mair DD. Acute postoperative obstruction of extracardiac conduit due to separation of thin fibrous peel *Mayo Clinic Proc* 1982; 57 189–91

2 Bharati S, Paul MH, Idriss FS, Potkin RT, Lev M The surgical anatomy of pulmonary atresia with ventricular septal defect: Pseudotruncus *J Thorac Cardiovasc Surg* 1975;69 713–21.

3 Chem DH, Moller JH. Comparison of late clinical status between patients with different hemodynamic findings after repair of tetralogy of Fallot. *Am Heart J* 1987;113:767–72.

4 Edwards WD, Agaraval KC, Feldt RH, Danielson GK, Puga FJ. Surgical pathology of obstructed right sided porcine valved extracardiac conduit. *Arch Pathol Lab Med* 1983,107:400–5

5 Fontan F, Choussat A, Devielle C, Doutremepuich C, Coupillaud J, Vosa C Aortic valve homografts in the surgical treatment of complex cardiac malformations *J Thorac Cardiothorac Surg* 1984;87 649–57

6 Kirklin JW, Blackstone EH, Shimazaki Y, Pacifico AD, Kirklin JK, Bargeron LM Survival, functional status and reoperation after repair of Tetralogy of Fallot with pulmonary atresia. *J Thorac Cardiovasc Surg* 1988;96:102–6.

7 Olin CL, Ritter DG, McGoon DC, Wallace RB, Danielson GK. Pulmonary atresia. Surgical considerations and results in 103 patients undergoing definitive repair. *Circulation* 1976;54 1135–40

8 Reid KG, Godman M, Burns J. Truncus arteriosus: successful surgical correction without the use of a valved conduit *Br Heart J* 1986;56 388–90

9 Borromee L, Lecompte Y, Batisse A, Lensoine G, Vouhe P, Sakata R, Leca F, Zamini L, Neveux JY. Anatomic repair of anomalies of ventriculoarterial connection associated with ventricular septal defect Clinical results in 50 patients with pulmonary outflow obstruction *J Thorac Cardiovasc Surg* 1988,95·96–102

10 Walsh EP, Rochenmacker S, Kane JF, Hougen TJ, Lock JE, Castaneda AR. Late results in patients with TOF repaired during infancy *Circulation* 1988;77 1062–7

CASE REPORTS

Fabry's disease with complete atrioventricular block: histological evidence of involvement of the conduction system

Yuji Ikari, Kenji Kuwako, Tetsu Yamaguchi

Abstract

A 63 year old man with complete atrioventricular block was diagnosed as having Fabry's disease. A short PR interval is a common electrocardiographic finding in Fabry's disease, but complete atrioventricular block is a very rare complication. Necropsy indicated that lipid accumulation in the atrioventricular conduction system was the probable cause of this patient's atrioventricular block.

(*Br Heart J* 1992;**68**:323–5)

Fabry's disease is an inherited disorder that causes glycosphingolipids to accumulate because of a deficiency of α-galactosidase A.[1] Cardiac involvement associated with left ventricular enlargement and supraventricular arrhythmias is quite common.[2-4] A short PR interval is a common electrocardiographic finding in Fabry's disease.[5] A few cases with complete atrioventricular block have been reported[6 7] but pathological studies of the conduction system were lacking. We report the necropsy findings in a patient with Fabry's disease associated with complete atrioventricular block.

Case report

A 63 year old man was admitted to Mitsui Memorial Hospital with dyspnoea on 2 February 1988. Two years before complete left bundle branch block and left axis deviation were diagnosed at another hospital (fig 1A). The PR interval was 0·16 s at that time. The day before admission he consulted a local doctor and the electrocardiogram showed complete atrioventricular block. The next day he was admitted to our hospital for investigation and treatment.

He had no history of painful paresthesia of the extremities, and no history of heat stroke during military training. An evaluation of his family history showed that four male cousins

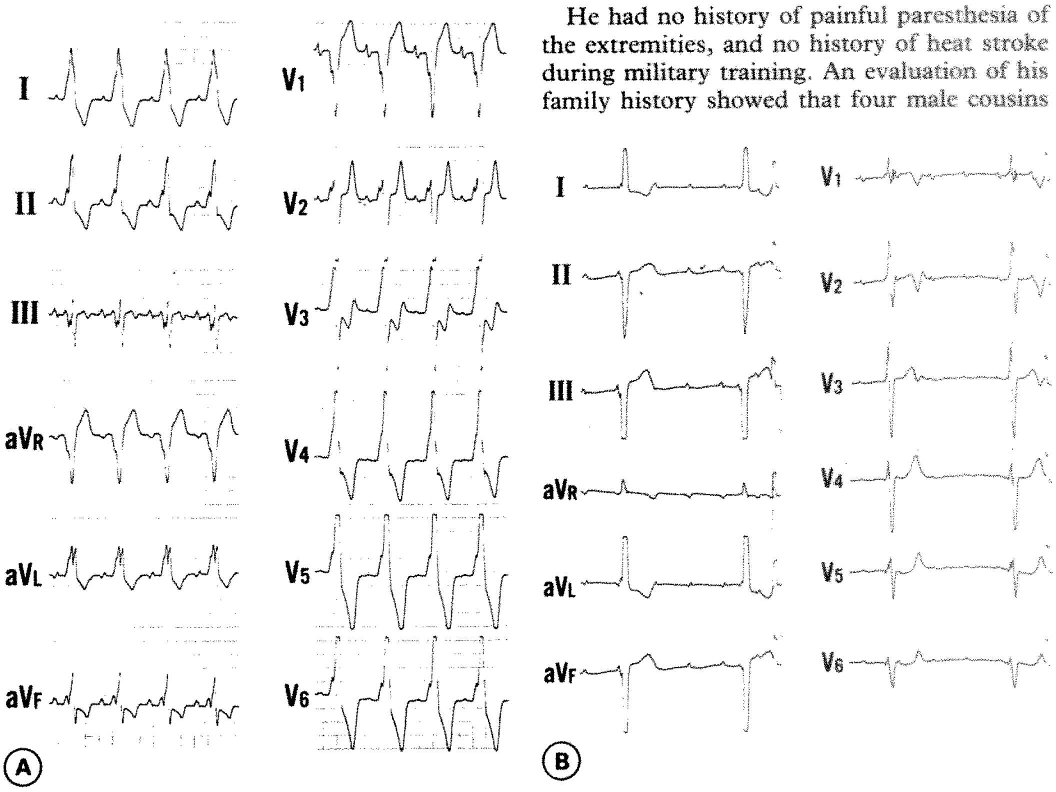


Figure 1 (A) An electrocardiogram taken two years before admission showed complete left bundle branch block, left axis deviation, and a normal PR interval (0·16 s). (B) On admission complete atrioventricular block and intraventricular conduction distrubance were found.

Division of Cardiology, Mitsui Memorial Hospital, 1, Tokyo, Japan
Y Ikari
K Kuwako
T Yamaguchi

Correspondence to
Dr Yuji Ikari, Mitsui Memorial Hospital,
1, Kandaizumi-cho,
Chiyoda-ku, Tokyo 101,
Japan.

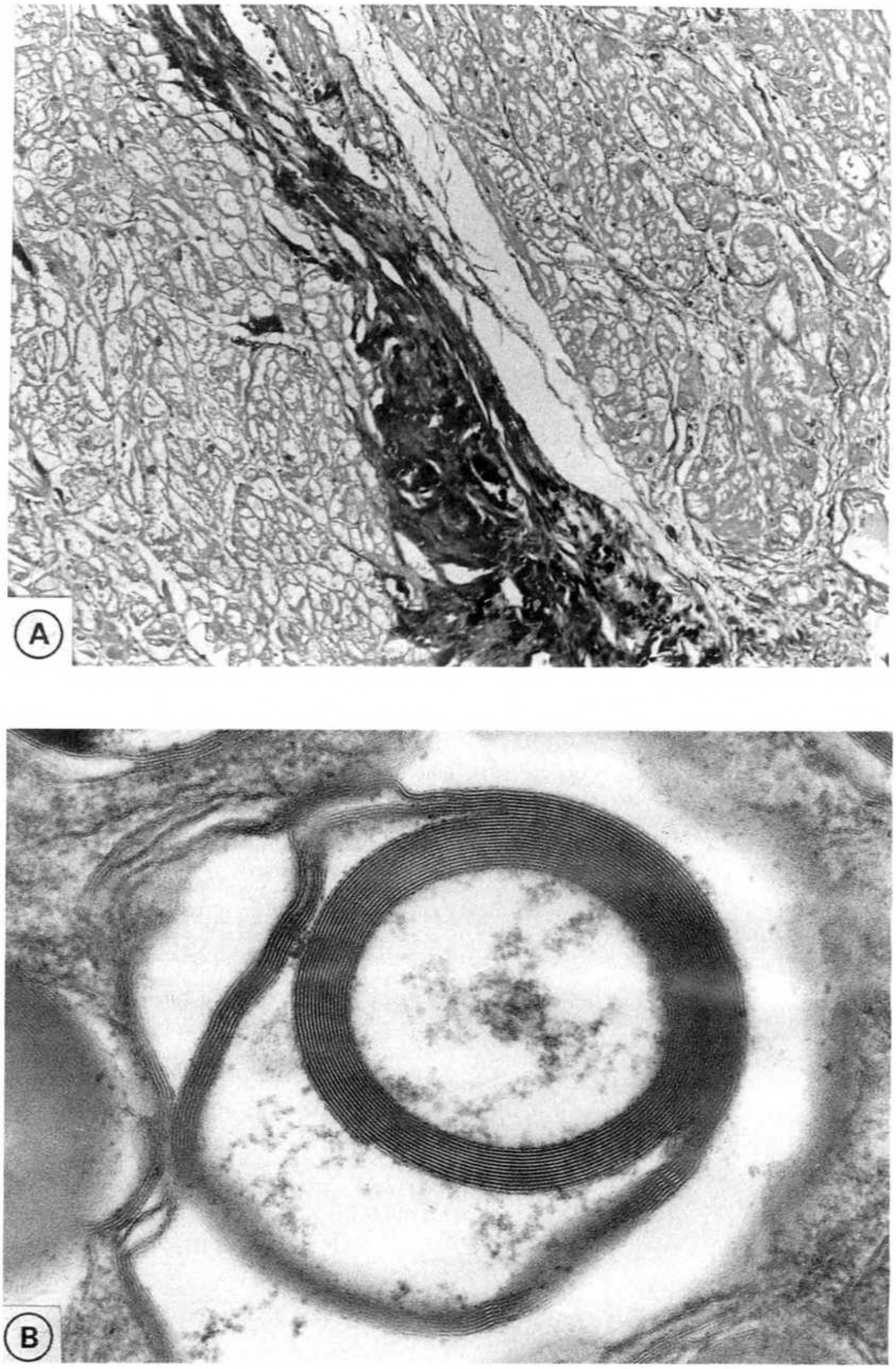


Figure 2 (A) Light micrograph showing diffuse vacuolar degeneration in the bundle of His (left) and adjacent myocardium (right) (elastic van Gieson Stain, original magnification × 200). (B) Electron micrograph showing that the hypertrophic myocardial cells contained concentric lamellar bodies (lead citrate and uranyl nitrate stain, original magnification × 130 000).

had died suddenly but no female relative had had cardiac disease.

On admission the pulse rate was 37 beats/min and regular and the blood pressure was 130/60 mm Hg. Inspiratory rales were audible at both lung bases and a third heart sound was heard at the apex. There was no oedema of the extremities. Cutaneous angiokeratomas similar to senile angiomas were seen. No cataracts were found.

The heart was enlarged (cardiothoracic ratio 67% on a chest x ray). The electrocardiogram showed complete atrioventricular block, left axis deviation, and intraventricular conduction defects (fig 1B). Laboratory studies indicated chronic renal failure and mild glucose intolerance. Blood urea nitrogen was 23·6 mmol/l, creatinine was 336 μmol/l, fasting plasma glucose was 10·1 mmol/l, and haemoglobin A_{1c} was 6·3%.

The echocardiogram showed left ventricular hypertrophy, left ventricular dilatation, and granular sparkling in the interventricular septum. Cardiac catheterisation and endomyocardial biopsy were performed, but coronary angiography was not done because of renal failure.

The mean pulmonary capillary wedge pressure was 23 mm Hg, the main pulmonary artery pressure was 59/20 (mean 30) mm Hg, the right ventricular pressure was 50/(end diastolic) 20 mm Hg, the mean right atrial pressure was 12 mm Hg, the left ventricular pressure was 165/(end diastolic) 45 mm Hg, and the aortic pressure was 170/65 mm Hg. Cardiac output was 4·6 l/min; and the cardiac index was 2·8 $l/min/m^2$. It was impossible to record the bundle of His electrocardiogram, presumably because the bundle voltage was too low.

In an endomyocardial biopsy specimen there was extensive deposition of osmophilic concentric lamellar bodies in the lysosomes. These lamellar bodies had a myelin-like configuration and represented the accumulation of glycosphingolipids. Biochemical studies showed that α-galactosidase A activity was appreciably decreased, though the activities of other lysosomal enzymes were normal. The diagnosis of Fabry's disease was thus confirmed. He improved after the implantation of a permanent pacemaker (Activitrax 8400, Medtronic, Minneapolis, MN 55432, USA) and the administration of oral frusemide.

A year and nine months later he was admitted again because of worsening heart failure and renal failure. Dobutamine, dopamine, and frusemide were administered, but he died of heart failure on 7 February 1990.

At necropsy biventricular hypertrophy (920 g/52 kg) and dilatation were found, but there was no evidence of myocardial infarction. Histological study showed severe diffuse vacuolar degeneration in the bundle of His, the branches of the bundle of His, and the ventricular myocardium, while degeneration of the sinoatrial node was relatively mild (fig 2). Moderate vacuolar degeneration and foamy macrophage infiltration of the renal glomerular epithelium were also seen.

Discussion

Cardiac involvement in Fabry's disease occurs by the progressive deposition of glycolipids, mainly ceramide trihexoside, in the myocardial cells. Left ventricular enlargement and supraventricular arrhythmias are quite common findings.[2–4]

A short PR interval in Fabry's disease has been described before. Roudebush *et al* reported three brothers with Fabry's disease and a short PR interval, and their review of 120 reported cases suggested that a short PR interval was a common finding.[5] In the electrophysiological study performed by Matsui *et al* the short PR interval was shown to be caused by a reduction in the A-H time with a normal H-V time.[8] The necropsy study by Becker *et al* showed glycosphingolipid deposits in the cells of the sinus node, the atrioventricular node, the bundle of His, and the left and right bundle banches.[2] They proposed that glycosphingolipid accumulation in the conduction system caused the short PR interval in this disease. Mehta *et al* reported that the PR interval was short in five out of 32 patients with Fabry's disease and prolonged in three of 13 patients on follow up examination.[6] They suggested that the prolongation was a result of progression of the disease process.

Complete atrioventricular block is rare in patients with Fabry's disease and only a few cases have been reported.[6,7] An electrophysiological study of two brothers performed by Suzuki *et al* indicated that one had a block within the bundle of His and the other had 2:1 atrioventricular block inthe atrioventricular node.[7] However, the cause of the atrioventricular block in their patients was not determined by a pathological study. Necropsy in our patient showed considerable deposition of glycosphingolipids in the bundle of His and bundle branches and no other pathological changes, suggesting that glycosphingolipid accumulation was the cause of his complete atrioventricular block. Complete atrioventricular block may be a terminal complication of Fabry's disease, with many patients apparently dying of renal failure before this cardiac defect can develop. Renal dysfunction in our patient progressed slowly and he lived until he was 65 years old; this gave time for the atrioventricular block to become apparent.

We thank Dr Hitoshi Sakuraba (Department of Clinical Genetics of the Tokyo Metropolitan Institute of Medical Science) for the enzyme assay, Dr Masao Nakahama and Dr Riichiro Takanashi for the pathological diagnosis, and Mr Ieharu Yamazaki for providing the electron photomicrographs.

1 Densick RJ, Bishop DF. Fabry's disease: α-galactosidase A deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic basis of inherited disease. 6th ed. New York: McGraw-Hill, 1989:1751–80.
2 Becker A, Schoorl FR, Balk A, Heide RM. Cardiac manifestations of Fabry's disease. *Am J Cardiol* 1975;**36**:829–35.
3 Desnick R, Bielden L, Sharp H, Hofschire P, Moller J. Cardiac valvular anomalies in Fabry's disease—clinical, morphologic, and biochemical studies. *Circulation* 1976;**54**:818–25.
4 Sakuraba H, Yanagawa Y, Igarashi T, *et al*. Cardiovascular manifestations in Fabry's disease. *Clin Genet* 1986;**29**:276–83.
5 Roudebush C, Foerster J, Bing O. The abbreviated PR interval of Fabry's disease. *N Engl J Med* 1973;**289**:357–8.
6 Mehta J, Tuna N, Moller JH, Densick RJ. Electrocardiographic and vectorcardiographic abnormalities in Fabry's disease. *Am Heart J* 1977;**93**:699–705.
7 Suzuki M, Goto T, Kato R, Yamauchi K, Hayashi H. Combined atrioventricular block and sinus node dysfunction in Fabry's disease. *Am Heart J* 1990;**120**:438–40.
8 Matsui S, Murakami E, Takekoshi N, *et al*. Cardiac manifestations of Fabry's disease: Report of a case with pulmonary regurgitation diagnosed on the basis of endomyocardial biopsy findings. *Jpn Circ J* 1977;**41**:1023–36.

Br Heart J 1992;68:326–9

Right-sided endomyocardial fibrosis with recurrent pulmonary emboli leading to irreversible pulmonary hypertension

P A Ribeiro, R Muthusamy, C M G Duran

Abstract

A 26 year old Saudi man with features of both Loeffer's endocarditis and endomyocardial fibrosis presented with mild symptoms and pulmonary emboli. Echocardiographic examination showed obliteration of the right ventricular apex by an attached mass. The results of haemodynamic studies were somewhat abnormal and medical treatment was started. Despite anticoagulation with warfarin the patient's condition deteriorated rapidly over a four month period after a further episode of pulmonary embolism and the development of pulmonary hypertension. Two haemodynamic studies performed four months apart were typical of pulmonary hypertension and later right ventricular failure; they showed none of the characteristics of restriction. Pulmonary embolectomy was attempted but there was no cleavage plane between the organised thrombi and the endothelium of the pulmonary artery. The patient died of severe pulmonary hypertension and right ventricular failure several days after operation.

Surgical intervention in the early stages of right-sided endomyocardial fibrosis might have prevented the development of pulmonary embolism and pulmonary hypertension.

(*Br Heart J* 1992;68:326–9)

Loeffer's endocarditis and endomyocardial fibrosis were long regarded as separate entities. Now Loeffer's endocarditis and endomyocardial fibrosis are generally regarded as manifestations of the same disease.[1–3] The pathological findings in advanced disease are identical for both conditions.[1–4] We describe a patient who had features of both Loeffer's endocarditis and endomyocardial fibrosis.

This patient presented at a relatively early stage of the disease when the right ventricle only was affected. At the time the patient had sustained a small pulmonary emboli and the haemodynamic function was somewhat abnormal. Despite anticoagulation with warfarin there were further episodes of pulmonary embolism and pulmonary hypertension and severe right heart failure developed. The surgical and pathological findings are described.

Case report

A 26 year old Saudi man living in Gizan was referred from the Riyadh Central Hospital for cardiac catheterisation. He had been complaining of dyspnoea and chest pain on exertion for the past six weeks. He was admitted after an episode of dizziness and chest pain at rest. The patient had had bronchial asthma from the age of five to the age of 16. He smoked 30 cigarettes a day. He had a rash eight years ago and a further two episodes of rash during the past two years. In November 1989 the jugular venous pulse was normal and the carotid upstrokes were normal. The chest was clear and blood pressure was 104/80 mm Hg. The pulse was 70 per minute and regular. The left ventricular impulse was normal and at auscultation a physiological split second heart sound was heard. P2 was normal. A pansystolic murmur (grade 1/4) was detected at the left sternal border. The liver was not palpable. There was no radiofemoral delay and all peripheral pulses were present with no bruits. There were no genital or mouth ulcers.

Echocardiographic studies showed obliteration of the right ventricular apex by a mass in the right ventricular cavity attached by a pedical (fig 1A). The patient was treated with intravenous heparin and was transferred to our hospital for further cardiac investigations. The full blood count was normal with 2% of eosinophils. The renal and liver profiles were normal. Protein electrophorisis showed a slight diffuse increase in γ globulins and the erythrocyte sedimentation was 11 mm/h. Protein C was 0·59 U/ml (normal between 0·64 and 1·13) and protein S was 0·37 U/ml (normal 0·51–0·91)—low and consistent with oral anticoagulation. Serological tests for schistosomiasis were negative. Antithrombin III was 90 mg/ml (normal = 80–120) and plasminogen 118 (normal = 80–120%). The partical thromboplastin time was 63 seconds while he was being given intravenous heparin. The chest *x* ray showed a heart of normal size and clear lung fields. The electrocardiogram showed sinus rhythm and incomplete right bundle branch block and non-specific ST-T changes. Holter monitoring showed periods of 2:1 atrioventricular block and a few ventricular extrasystoles. Echocardiographic studies showed a left ventricle of normal size and function. The right atrium was dilated and an irregular mass obliterated the right ventricular apex and extended to half way up the ven-

Department of Cardiovascular Diseases, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
P A Ribeiro
R Muthusamy
C M G Duran

Correspondence to
Dr P A Ribeiro, MBC 16,
King Faisal Specialist
Hospital, PO Box 3354,
Riyadh 11211, Saudi Arabia

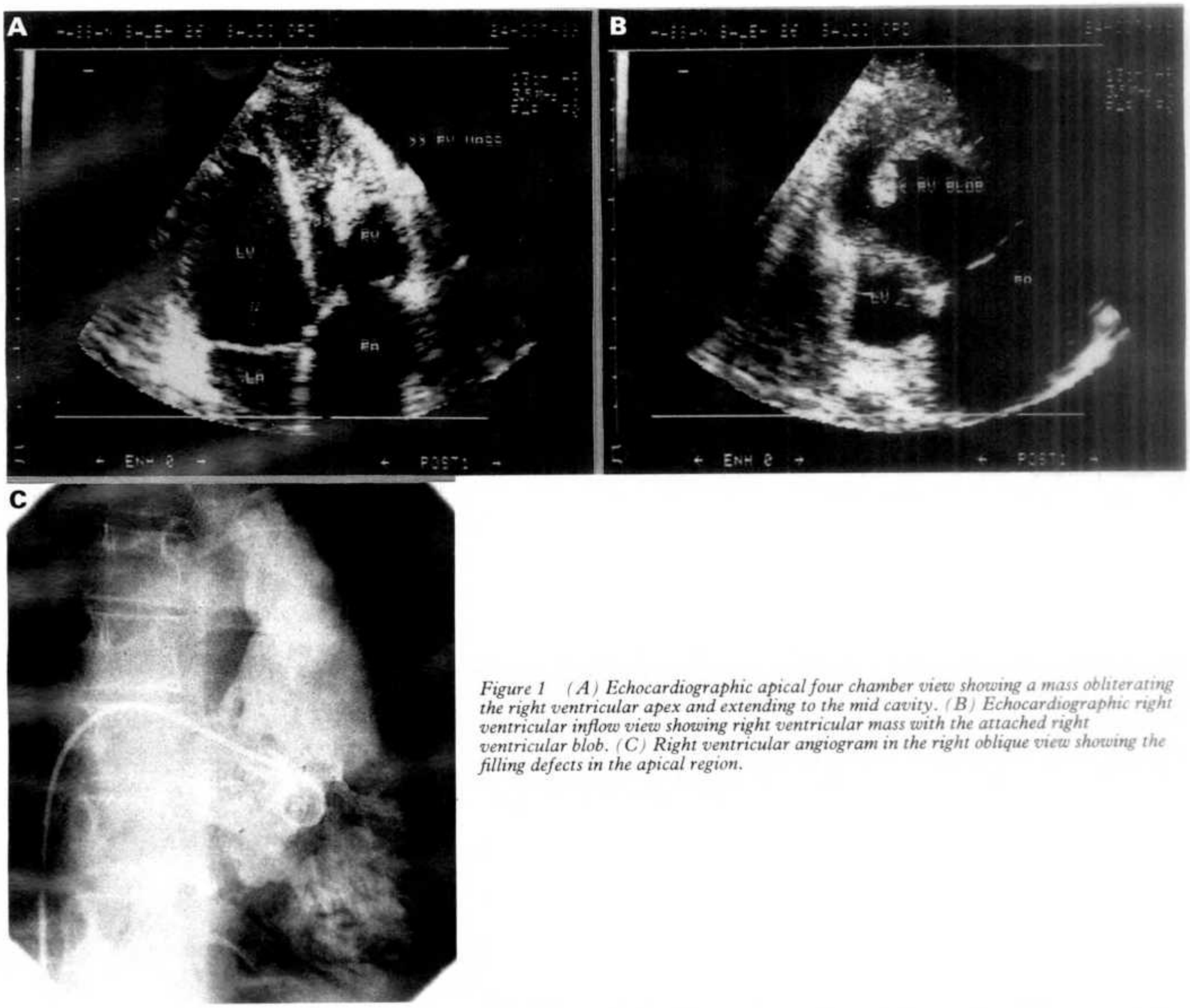


Figure 1 (A) Echocardiographic apical four chamber view showing a mass obliterating the right ventricular apex and extending to the mid cavity. (B) Echocardiographic right ventricular inflow view showing right ventricular mass with the attached right ventricular blob. (C) Right ventricular angiogram in the right oblique view showing the filling defects in the apical region.

tricular cavity (figs 1 and 2). Colour Doppler showed moderate tricuspid regurgitation. Cardiac catheterisation showed no haemodynamic evidence of constrictive or restrictive physiology or both. The mean right atrial pressure was 8 mm Hg with an 'a' wave of 13 and a 'v' wave of 10 mm Hg. The right ventricular pressure was 33/3 mm Hg and the pulmonary artery pressure was 33/19 (mean 24) mm Hg. Pulmonary capillary wedge was 7 mm Hg and left ventricular pressure 104/12 mm Hg. The left ventricular angiogram was normal. The right ventriculogram showed moderate tricuspid regurgitation and a dilated right ventricular cavity. There were filling defects in the right ventricular apex (not a typical feature of endomyocardial fibrosis) without evidence of right ventricular apex cut off (fig 1C). The pulmonary angiogram showed occlusion of the pulmonary arteries supplying the left, mid and lower lobes (fig 2A). A biopsy specimen of the right ventricle taken in November 1989 showed a thrombus containing degranulated eosinophils with minimal myocardial fibrosis. At this stage the diagnosis was early stage endomyocardial fibrosis with pulmonary emboli. Because the symptoms were mild and cardiac haemodynamics function virtually normal we decided to continue anticoagulation treatment with warfarin. Beçhet's disease was excluded and the cardiac biopsy specimen, though not pathognomonic, indicated endomyocardial fibrosis. The patient was followed up in the outpatient clinic and warfarin anticoagulation was regularly monitored (prothrombin time ratio of 2:1).

In January 1990 the patient was reviewed in the outpatient clinic and was still doing well and the echocardiographic study showed evidence of a right ventricular mass (figs 1 and 2). From then onwards there was a gradual clinical deterioration and in March 1990 the patient was unwell. During the past month he deteriorated considerably and was now in New York Heart Association Class IV with shortness of breath on minimal exertion and orthopnoea. When the patient was admitted the jugular venous pulse was raised to the angle of the jaw. The heart rate was 85 beats/min and regular. There was a pansystolic murmur grade 3/4 at the sternal border and a striking gallop rhythm. The liver was palpable 4 cm below the costal grade. There was ascites. The electrocardiogram showed right axis deviation and evidence of right ventricular hypertrophy and right bundle branch block. Echocardiographic studies showed a persistent right ventricular mass and severe tricuspid regurgitation (figs 1A

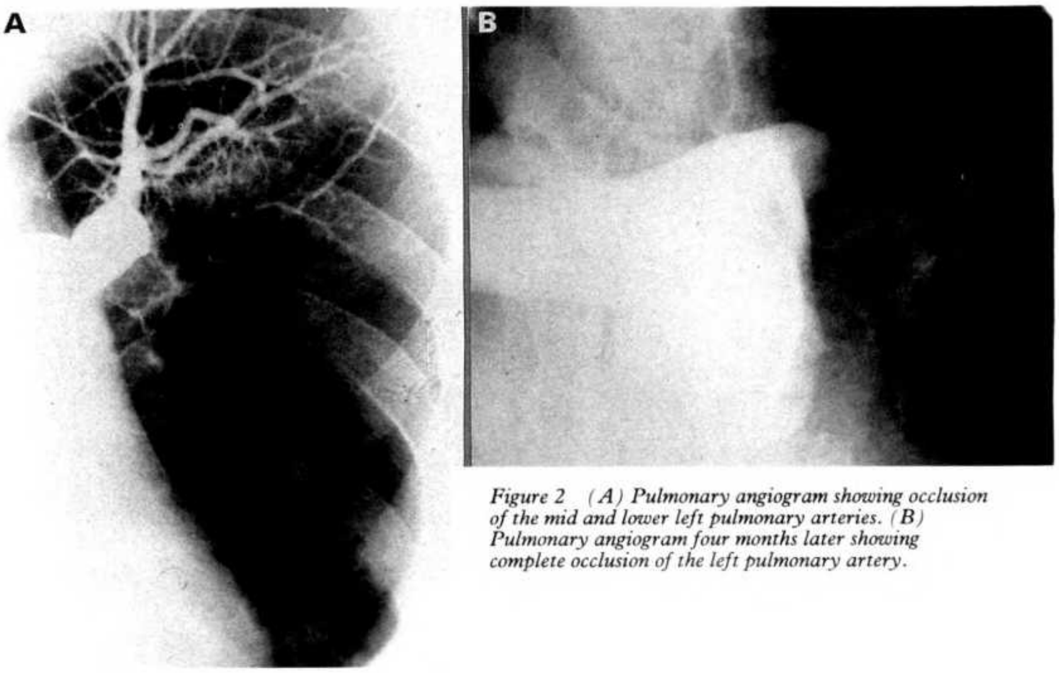


Figure 2 (A) Pulmonary angiogram showing occlusion of the mid and lower left pulmonary arteries. (B) Pulmonary angiogram four months later showing complete occlusion of the left pulmonary artery.

and B). Repeat cardiac catheterisation showed major deterioration in the haemodynamic function of the right side of the heart. The mean right atrial pressure had increased to 15 mm Hg with an 'a' wave of 18 mm Hg and a 'v' wave of 20 mm Hg. Right ventricular pressure was 45/12 and pulmonary artery 48/22 mm Hg (mean 38). The cardiac output was 2·2 l/min with an index of 1·2 l/min/m^2. Pulmonary angiography showed a total block of the left pulmonary artery and a filling defect in the right middle pulmonary artery (fig 2B).

In view of the patient's severe symptoms and rapid haemodynamic deterioration, which were caused by further pulmonary emboli, we decided to attempt to excise the right ventricular mass and perform a pulmonary embolectomy. At operation the posterior and septal leflets of the tricuspid valve were tethered by the fibrous tissue that was a continuation of the papillary muscle. The apical and septal mass was seen in the right ventricle. The mass was whitish and fibrous strands penetrated into the myocardium, which was ulcerated and covered in thrombus. The mass extended to the outflow tract of the right ventricle. The left pulmonary artery was occluded with a recent thrombus, superimposed on old fibrous whitish material that was completely attached to the endothelium of the pulmonary artery. There was no cleavage plane.

The right ventricular mass was excised and the tricuspid valve was replaced by a Hancock 33 bioprosthesis. Embolectomy was impossible because the whitish material of the pulmonary artery was attached to the endothelium. Left pneumectomy was performed because there was considerable bleeding in the endotracheal tube during weaning of bypass. The patient was transferred to the intensive care unit in a reasonable condition. After being extubated on the third postoperative day respiratory acidosis developed and the patient required reintubation. He sustained a cardiac arrest that required open chest massage in the intensive care unit and he was transferred to the operating room and put on cardiopulmonary bypass. Attempts at weaning him off bypass failed because the right ventricle was distended and the pulmonary artery pressure was above systemic level. The patient was given extra-corporeal membrane oxygenation and biomedical support. After 10 hours of right-sided bypass the pulmonary artery pressure was still suprasystemic and there were no signs of recovery. Several attempts at weaning him off bypass were unsuccessful and the patient died in the operating room. The pathological and histological examination of the specimens of the right ventricle and left pulmonary artery showed features that were characteristic of endomyocardial fibrosis with superimposed thrombus.

Discussion

Our patient had features that were typical of both Loeffer's endocarditis and endomyocardial fibrosis.[5-9] His history of asthma, rash, multiple pulmonary emboli, is characteristic of Loeffer's disease. The absence of peripheral eosinophils, isolated right ventricular disease, and absence of systemic illness are features of endomyocardial fibrosis. Although endomyocardial fibrosis and Loeffer's disease used to be regarded as separate clinical entities there is a growing consensus that they are different stages of the same disease.[1-4] Our patient was probably in an intermediate stage of the diseases.

The right ventricle alone is affected in 10% of cases of endomyocardial fibrosis.[10] The restrictive physiology is the haemodynamic hallmark of the disease.[10] Our patient, however, presented with normal haemodynamic function and without the features of restriction, despite the large right ventricular mass detected on echocardiography. Despite appropriate anticoagulation the disease progressed rapidly with further pulmonary emboli and pulmonary hypertension with right ventricular failure developed. This contrasts with the usual pattern when right heart failure is caused by restriction of the right ventricle.[10]

The course in our patient suggests that earlier excision of the right ventricular mass might have prevented further pulmonary emboli. Medical treatment with anticoagulation did not prevent the progression of the disease to fatal pulmonary embolism. The initial angiogram was misleading because it did not show the classic ventricular apex cut off of endomyocardial fibrosis. When we reviewed the angiogram we found some filling defects that others have described as early evidence of endomyocardial fibrosis.[11] Nevertheless, the echocardiographic appearance at the time showed a large apical mass extending to the middle of the right ventricle cavity. Colour Doppler examination showed some blood flow to the right ventricular apex in between the mass and this accounted for the angiographic appearance. The nuclear magnetic resonance examination accorded with echocardiographic findings.

We conclude that early surgical intervention may be indicated in the early stages of endomyocardial fibrosis/Loeffer's disease with right-sided involvement to prevent pulmonary emboli and the development of pulmonary hypertension.

1 Roberts WC, Buja LM, Ferran VJ. Loeffler's fibroplastic parietal endocarditis, eosinophilic leukemia, a Davies endomyocardial fibrosis: The same disease at different states. *Pathol Microbiol* 1970,35:90–5.
2 Davies J, Spry CJF, Viyaya Raghaven G, Desousa JA. A comparison of the clinical and cardiological features of endomyocardial disease in temperate and tropical regions. *Postgrad Med J* 1983;59.179–86.
3 Olsen EG. Pathological aspects of endomyocardial fibrosis. *Postgrad Med J* 1983;59·135–42
4 Roberts WC, Liegeler DG, Carbone PP. Endomyocardial disease and eosinophilic. A clinical and pathologic spectrum. *Am J Med* 1969;48 28–42.
5 Spry CJ. The hypereosinophilic syndrome. Clinical features, laboratory findings and treatment *Allergy* 1982; 37:539–46.
6 Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic and therapeutic considerations *Ann Intern Med* 1982, 97:78–92.
7 Davies JNP, Coles RM. Some considerations regarding obscure disease affecting the normal endocardium. *Am Heart J* 1960;59:606–10.
8 Cherian KM, John TA, Abraham KA. Endomyocardial fibrosis clinical profile and role of surgery in management *Am Heart J* 1983,105:706–10.
9 Fawzy ME, Halim M, Ziady G, Guindy R, Mercer EN, Feteih N. Endomyocardial fibrosis. Report of eight cases. *J Am Coll Cardiol* 1985,5 983–89.
10 Cardiomyopathies Geneva World Health Organization 1984.
11 Sasidharan K, Kartha CC, Balkrishnan KG, Valiathan MJ Early angiographic features of right ventricular endomyocardial fibrosis. *Cardiology* 1985;70 127–31.

Br Heart J 1992;**68**:330–2

Anomalous origin of the right coronary artery from the pulmonary artery in association with congenital aneurysm of the sinus of Valsalva: angiographic diagnosis of a rare association

A Shyam Sundar, Keith A A Fox

Abstract

A 37 year old man presenting with acute heart failure, hypotension, and acute renal failure was diagnosed by cardiac catheterisation and angiography to have the rare combination of congenital aneurysm of the non-coronary sinus of Valsalva rupturing into the right ventricle, and an anomalous origin of the right coronary artery from the main pulmonary artery. The diagnosis could not be confirmed by transthoracic echocardiography in this patient. This combination of defects, confirmed at cardiac surgery, has not been reported before, and this case report highlights the importance of preoperative definition of congenital defects associated with an aneurysm of the sinus of Valsalva.

(*Br Heart J* 1992;**68**:330–2)

Anomalous origin of the right coronary artery from the main pulmonary artery is a rare congenital cardiac malformation.[1 2] Twenty five cases with this condition have been reported to date, most as incidental findings, at necropsy, or during surgery; a few have been diagnosed by angiography.[3] Congenital aneurysms of the sinus of Valsalva are comparatively rare[4 5] and may be associated with other anomalies including ventricular septal defect, aortic valve, and coronary artery anomalies.[6 7] To the best of our knowledge, there have been no reported instances of anomalous origin of a right coronary artery from the pulmonary artery in association with congenital aneurysm of the sinus of Valsalva.

We report the preoperative diagnosis, by cardiac catheterisation and angiography, of the rare combination of ruptured aneurysm of the sinus of Valsalva and anomalous right coronary artery from the pulmonary artery in a 37 year old man presenting with acute heart failure, hypotension, and acute renal failure. The findings were confirmed at surgery.

Department of Cardiology, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN
A Shyam Sundar
K A A Fox

Correspondence to:
Professor Keith A A Fox,
The Duke of Edinburgh Professor of Cardiology,
Cardiovascular Research Unit, University of Edinburgh, Hugh Robson Building, George Square,
Edinburgh EH8 9XF.

Case report

A 37 year old man presented with a sudden illness. He had had a 48 hour history of palpitations followed by dyspnoea, recurrent vomiting, and anuria, and was admitted in acute renal failure and cardiogenic shock. He had previously felt entirely well and went swimming for 30 minutes, two days before admission to hospital. He had had no significant illness in the past and had no history of chest pain. On clinical examination, the patient was pale, cyanosed, tachypneic, and was hypotensive with wide pulse pressure and sinus tachycardia. He was in cardiac failure with raised jugular venous pressure, tender hepatomegaly, and bibasal chest crackles.

Cardiovascular examination showed cardiomegaly with a forcible cardiac impulse. There was a superficial continuous murmur (grade 3/6) heard at the lower left sternal border. The electrocardiogram showed sinus tachycardia without evidence of ventricular hypertrophy or myocardial ischaemia. The chest radiograph showed mild cardiac enlargement and pulmonary plethora. He was treated with ionotropes and haemofiltration followed by regular dialysis for control of his renal failure. He underwent transthoracic echocardiographic studies but high quality recordings could not be obtained because of his chest configuration.

Cardiac catheterisation showed raised right heart pressures with moderate pulmonary arterial hypertension (50/25 mean 35

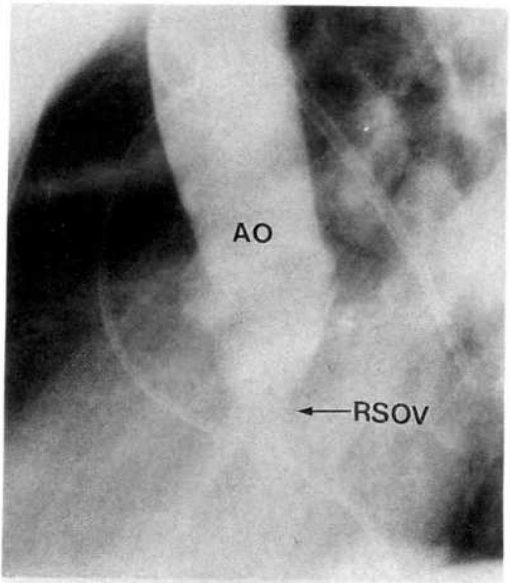


Figure 1 Aortogram (left lateral projection) showing ruptured aneurysm of the non-coronary sinus of Valsalva with a leak into the right ventricle. AO, aorta; RSOV, aneurysm of the ruptured sinus of Valsalva.

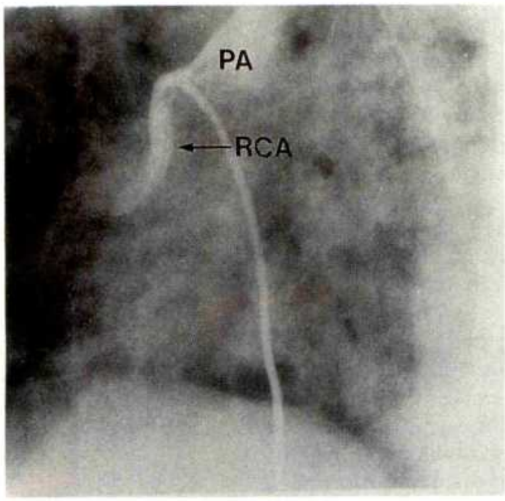


Figure 2 Selective angiogram from main pulmonary artery showing anomalous pulmonary origin of the right coronary artery. PA, main pulmonary artery; RCA, right coronary artery.

mm Hg). There was a step up in oxygen saturation in the right ventricle with a left to right shunt of 4:1. Aortic root angiography showed an aneurysm of the non-coronary sinus of Valsalva rupturing into the right ventricle (fig 1). Coronary angiography showed a normal left coronary artery with collaterals to the right coronary artery. The large right coronary artery filled retrogradely from the left system and showed flow of contrast material into the main pulmonary artery from which it originated. Anomalous pulmonary origin of the right coronary artery was documented by selective cineangiography from the main pulmonary artery (fig 2). The patient also had a patent foramen ovale and a left superior vena cava draining into the coronary sinus.

The patient underwent successful operation and at surgery, the findings of ruptured aneurysm of the non-coronary sinus of Valsalva opening into the right ventricle and anomalous origin of the right coronary artery from the main pulmonary artery were confirmed. The aneurysm of the sinus of Valsalva produced the previously described "windsock" deformity and was excised, leaving a slit-like defect between the aortic wall and the aortic annulus. This was closed with sutures. The anomalous right coronary artery could not be seen on external inspection but subsequent dissection and exploration showed it to arise from the right side of the pulmonary artery and it was reimplanted into the ascending aorta. No heart murmurs were heard in the postoperative period. Renal function gradually recovered to normal and a repeat Swan Ganz catheterisation six weeks after operation showed normal pressures and oxygen saturation. The patient is currently symptom free 18 months after operation.

Discussion

Aneurysms of the sinus of Valsalva are rare, accounting for 0·43% and 0·14% of open heart operations done at two major cardiac surgical centres.[4 5] They are frequently associated with other congenital cardiac defects such as ventricular septal defect and aortic valve anomalies.[6] Anomalies of the coronary artery may complicate the surgical repair especially when only discovered at operation for rupture of the aneurysm of the sinus of Valsalva. For example, a single coronary artery was discovered at operation when coronary angiography was not performed.[7]

Although aneurysms of the sinus of Valsalva may be detected by echocardiography, in subjects in whom high quality recordings are obtainable, this case report shows the clinical importance of defining any associated congenital anomalies. Unless such concomitant lesions can be defined by echocardiography, it may be necessary to undertake angiography in patients with ruptured aneurysm of the sinus of Valsalva.

Echocardiography is a useful non-invasive tool in diagnosing aneurysms of the sinus of Valsalva.[8] Cross sectional and Doppler echocardiography, however, even in experienced hands, have missed such aneurysms, which were subsequently diagnosed by cardiac catheterisation and confirmed at surgery.[9] Despite a clinical diagnosis before echocardiography of a ruptured aneurysm of the sinus of Valsalva, the transthoracic echocardiographic recordings were inadequate to confirm the diagnosis in this compromised and poorly echogenic subject. Transoesophageal echocardiography, with Doppler colour flow mapping, would be the investigation of choice for such suspected ruptures, particularly where transthoracic recordings are inadequate.[10] This would not, however, have shown the associated anomaly of the coronary artery. Transoesophageal echocardiography was not available to us when this patient presented.

The definitive diagnosis of ruptured aneurysm of the sinus of Valsalva can be established by cardiac catheterisation and angiography, as can associated cardiac defects detected, including anomalies of the coronary artery.

Anomalous origin of the right coronary artery from the main pulmonary artery is extremely rare with a reported incidence of 0·002% in a series of 126 595 patients undergoing coronary angiography over a 28 year period at the Cleveland Clinic Foundation.[11] Twenty five reported cases are available for review.[12–14] Isolated cases of patients with associated congenital heart disease, including atrial septal defect, tetralogy of Fallot with patent ductus arteriosus, pulmonary atresia with intact ventricular septum, and aortopulmonary window with and without ventricular septal defect have been reported.[2 3 13 14] An anomalous origin of the right coronary artery from the pulmonary artery, as far as we know, has not been previously described in association with congenital aneurysm of the sinus of Valsalva.

By contrast with patients who have the far more common condition of anomalous pulmonary origin of the left coronary artery and who often present in infancy with ischaemia and congestive heart failure,[3] most patients with anomalous origin of the right coronary artery are symptom free and reach adult life. Anomalous origin of the right coronary artery, however, is not always a benign condition. There have been reports of sudden cardiac death[2 15] and a coronary steal phenomenon whereby the right ventricle and inferior and septal regions of the left ventricle were deprived of blood supply due to retrograde flow from the left coronary artery to the pulmonary artery through the anomalous right coronary artery.[16] Our patient showed neither symptoms nor electrocardiographic evidence of myocardial ischaemia. Nevertheless, the fact that anomalous origin of right coronary artery from the pulmonary artery is a cause of cardiac arrest may justify prophylactic surgical intervention, if this coronary anomaly is known to be present.

The acute development of a large rupture in the aneurysm of the sinus of Valsalva probably accounted for the dramatic presentation in our patient. As a result of the anomalous large right coronary artery, however, ischaemia of right ventricle and posteroinferior regions of the left ventricle could have contributed to the development of heart failure.

Our patient highlights the usefulness of cardiac catheterisation and angiography in the accurate preoperative delineation of this rare combination of lesions that were confirmed at surgery.

We gratefully acknowledge the surgical expertise of Mr E G Butchart and Mr A J Bryan in the management of this patient.

1 Roberts WC. Major anomalies of coronary arterial origin seen in adulthood. *Am Heart J* 1986,111.941–63

2 Lerberg DB, Ogden JA, Zuberbuhler JR; Bahnson HT. Anomalous origin of the right coronary artery from the pulmonary artery *Ann Thorac Surg* 1979;27:87–94.

3 Neufeld HN, Schneeweiss A. Anomalous origin of the coronary arteries from the pulmonary artery. In: Neufeld HN, Schneeweiss A, eds *Coronary artery disease in infants and children*. Philadelphia: Lea and Febiger, 1983:1–30.

4 Meyer J, WuKasch DC, Hallman GL, Cooley DA. Aneurysm and fistula of the sinus of Valsalva *Ann Thorac Surg* 1975,19:170–9.

5 Henze A, Huttunen H, Bjork VO. Ruptured sinus of Valsalva aneurysms. *Scan J Thorac Cardiovasc Surg* 1983;17:249–53.

6 Nowicki ER, Aberdeen E, Friedman S, Rashkind WJ. Congenital left aortic sinus-left ventricular fistula and review of aortocardiac fistulas. *Ann Thorac Surg* 1977; 23:378–88.

7 Chamsi-Pasha H, Gandhi RG, Logan WFW. Ruptured aneurysm of sinus of Valsalva co-existing with a single coronary artery. *Eur Heart J* 1989;10:180–1.

8 Sahasakul Y, Panchavinnin P, Chaithiraphan S, Sakiyalak P. Echocardiographic diagnosis of a ruptured aneurysm of the sinus of Valsalva: operation without catheterisation in seven patients. *Br Heart J* 1990;64:195–8

9 Chiang CW, Lin FC, Fang BR, Kuo CT, Lees YS, Chang CH. Doppler and two-dimensional echocardiographic features of sinus of Valsalva aneurysm. *Am Heart J* 1988,116:1283–8

10 Abdelkhirane C, Roudaut R, Dallocchio M. Diagnosis of ruptured sinus of Valsalva aneurysms: Potential value of transesophageal echocardiography. *Echocardiography* 1990;7:555–60.

11 Yamanaka O, Hobbs RE Coronary artery anomalies in 126 595 patients undergoing coronary arteriography *Cathet Cardiovasc Diagn* 1990,21:28–40.

12 Mahdyoon H, Brymer JF, Alam M, Khaja F. Anomalous right coronary artery from the pulmonary artery presenting with angina and aneurysmal left ventricular dilatation. *Am Heart J* 1989,118:182–4.

13 Brouwer MHJ, Beaufort-Krol GCM, Talsma MD Aortopulmonary window associated with an anomalous origin of the right coronary artery. *Int J Cardiol* 1990;28:384–6.

14 Gerlis LM, Ho SY, Milo S. Three anomalies of the coronary arteries co-existing in a case of pulmonary atresia with intact ventricular septum. *Int J Cardiol* 1990,29:93–5.

15 Wald S, Stonecipher K, Baldwin BJ, Nutter DO. Anomalous origin of the right coronary artery from the pulmonary artery. *Am J Cardiol* 1971;27:677–81.

16 Mintz GS, Iskandarian AS, Bernis CE, Mundth ED, Owens JS. Myocardial ischemia in anomalous origin of the right coronary artery from the pulmonary trunk. *Am J Cardiol* 1983;51:610–2

Br Heart J 1992;**68**:333–8

TECHNOLOGY

Cardiac assistance from skeletal muscle: a critical appraisal of the various approaches

Stanley Salmons, Jonathan C Jarvis

Abstract

We review here various ways in which cardiac assistance might be derived from a patient's own skeletal muscle. Calculations based on experimental data and optimistic estimates of the efficiency of the energy conversions involved suggest that the continuous assist available would be limited to about 2 litres a minute if a muscle were used to energise an electromechanical device. It would be more efficient to couple the energy mechanically or hydraulically, but these approaches still pose problems of anatomical placement, muscle attachment, fluid leakage, and cost. Unless these issues can be addressed, the use of skeletal muscle as an internal power source for mechanical circulatory assist devices will remain an unworkable concept. Configurations that couple skeletal muscle contraction directly to the circulation would be more efficient and less costly. In terms of the energy available, a skeletal muscle ventricle could be designed to provide a continuous partial assist of 1–2 l/min, with flows of up to 8 l/min sustainable for limited periods. Such an approach offers new possibilities for the surgical treatment of chronic cardiac failure.

British Heart Foundation Skeletal Muscle Assist Research Group, Department of Human Anatomy and Cell Biology, University of Liverpool, Liverpool
S Salmons
J C Jarvis

Correspondence to Professor S Salmons, British Heart Foundation Skeletal Muscle Assist Research Group, Department of Human Anatomy and Cell Biology, PO Box 147, University of Liverpool, Liverpool L69 3BX.

Accepted for publication 1 May 1992

(*Br Heart J* 1992;**68**:333–8)

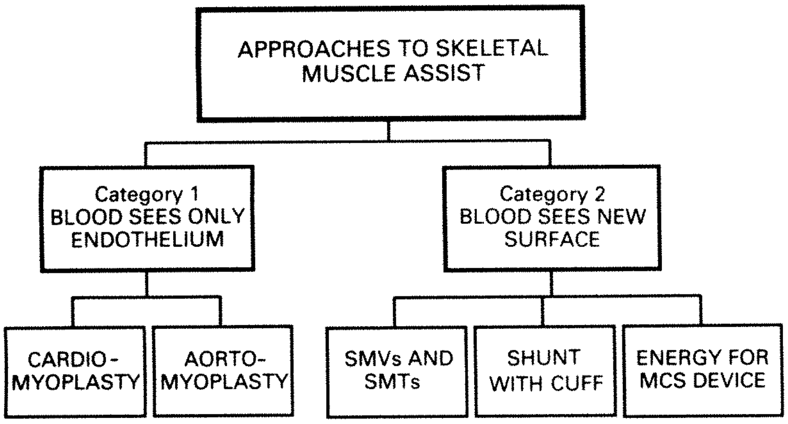

APPROACHES TO SKELETAL MUSCLE ASSIST
Category 1 BLOOD SEES ONLY ENDOTHELIUM
Category 2 BLOOD SEES NEW SURFACE
CARDIO-MYOPLASTY
AORTO-MYOPLASTY
SMVs AND SMTs
SHUNT WITH CUFF
ENERGY FOR MCS DEVICE

Figure 1 Alternative approaches to the use of skeletal muscle for cardiac assistance. MCS, mechanical circulatory support; SMV, skeletal muscle ventricle; SMT, skeletal muscle tube ventricle.

For some years the surgical treatment of end stage cardiac failure has been restricted to cardiac transplantation and the temporary use of mechanical circulatory support devices as a bridge to transplant. The discovery that adult fast-twitch mammalian skeletal muscle is capable of undergoing adaptive change, through which it can acquire a markedly increased resistance to fatigue, has revived interest in the possibility of diverting skeletal muscle from its normal function to perform in a cardiac assist role.

The adaptive transformation of skeletal muscle that takes place in response to increased use has been studied extensively[1-3] and it is not proposed to describe it in any detail here. The important elements can, however, be stated quite simply. A muscle will be resistant to fatigue if it can supply, on a continuous basis, sufficient ATP to meet the prevailing energy costs of contraction. These costs derive mainly from the cyclic turnover of chemical bonds between actin and myosin and the transport of calcium between intracellular compartments. Skeletal muscle that has been conditioned by long-term electrical stimulation acquires more favourable bioenergetics for sustained contraction as a result of changes both in the isoforms of myosin and in the kinetics of the release and uptake of calcium. At the same time, sustained production of ATP becomes possible through an increase in the capacity of oxidative pathways, particularly those involved in the breakdown of fat and fatty acids, at the expense of anaerobic glycolysis. There is an associated increase in capillary blood supply and mitochondrial volume. As a result, the production of ATP can match even the extreme increases in the utilisation of ATP required for the performance of cardiac work.[4-6]

Four approaches to skeletal muscle assist

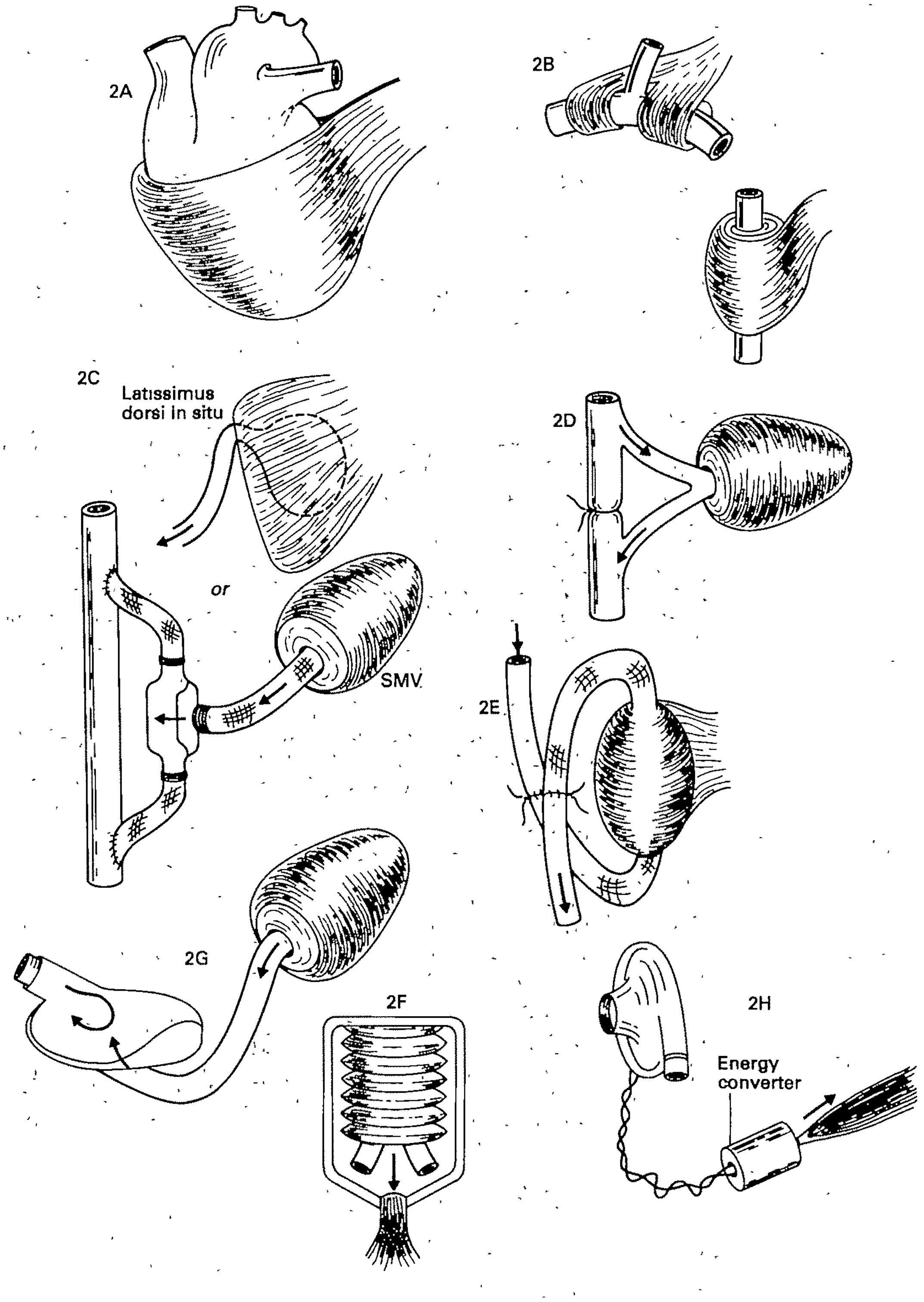
There are several ways in which we can try to harness the power of conditioned skeletal muscle for cardiac assistance but they fall into two major categories (fig 1).

CATEGORY 1 ASSISTS

These preserve the natural endothelial lining of the patient's cardiovascular system. There are two main approaches:

(*a*) In cardiomyoplasty, the object is to

Figure 2 Highly schematic examples to illustrate the approaches listed in fig 1: (A) cardiomyoplasty, (B) aortomyoplasty, (C) compression of aorta by a cuff, (D) skeletal muscle ventricle, (E) skeletal muscle tube ventricle, (F) left ventricular assist device (LVAD) energised mechanically, (G) LVAD energised hydraulically, (H) LVAD energised electrically.



produce intermittent compression of the patient's left or right ventricle by the contraction of skeletal muscle wrapped around the organ[7 8] (fig 2A).

(*b*) In aortomyoplasty, the ascending or descending aorta may be wrapped directly[9] (fig 2B); alternatively, compression may be achieved indirectly by arranging for contraction of the muscle to inflate a cuff placed around the vessel[10] (fig 2C).

From one point of view, category 1 assists are the most conservative option, since the presence of an uninterrupted endothelium minimises the risk of thromboembolic complications. Small wonder, then, that cardiomyoplasty is the first, and so far the only, approach to have been used clinically.

CATEGORY 2 ASSISTS

These form part of an independent structure that is connected to the patient's circulation. As a result, an additional surface—which may be an artificial material or an autogenous biological lining—is placed in contact with the blood. Again there are two main approaches:

(*a*) Skeletal muscle can be configured as an auxiliary pouch-shaped or tube-shaped ventricle by wrapping it around a suitable mandrel;

the mandrel is subsequently removed, leaving a skeletal muscle ventricle (SMV) (fig 2D) or a skeletal muscle tube ventricle (SMT) (fig 2E) that can be connected to the circulation as a synchronous or counterpulsatory assist.[4,11,12]

(*b*) Skeletal muscle may be used to energise a mechanical artificial heart or ventricular assist device via a mechanical (fig 2F), hydraulic (fig 2G), or electrical (fig 2H) link.[13,14]

The fundamental limitation on the assists that can be obtained through these various approaches is the rate at which they allow energy to be converted to pumping work. We therefore consider first the power *required* for cardiac assistance. We go on to use recent experimental data from this laboratory to estimate the power *available* from skeletal muscle under ideal conditions. Finally we estimate the power that could be *transferred* into the circulation by the different configurations, and add comments on some of the practical difficulties.

How much power is needed for cardiac assistance?

The power required for pumping is related to the flow and the mean pressure by the expression:

Power = flow × pressure

For a normal 70 kg subject with a body surface area of $1{\cdot}7\ m^2$ the mean flow at rest is about 6 l/min.[15] For an average systemic pressure of 100 mm Hg this corresponds to about 1·3 W. A capacity for at least 14 l/min should be built into the pump to support activities such as walking and climbing stairs, and it would therefore be appropriate to specify a short-term power capability of at least 3 W. These levels are necessary where the patient's heart is in such poor condition that most of the systemic blood flow must be produced by the assist device. In less severe cases it may be acceptable to operate at lower levels, providing partial assistance that restores a reasonable quality of life while improving, or at least preventing further deterioration in, the condition of the patient's own heart.

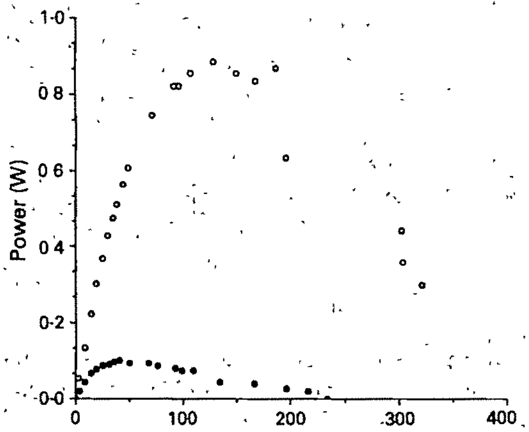


Figure 3 Graph showing the relation between power output and velocity of shortening for the left (filled circles) and right (open circles) tibialis anterior muscles of a rabbit. The left muscle had received 8 weeks of continuous stimulation at 10 Hz.

How much power is available?

No artificial energy source currently available can provide these levels of power from within the body. As a biological source, skeletal muscle has attracted interest because it allows a small expenditure of energy (needed to stimulate the motor nerve) to trigger the release of a potentially large amount of energy (derived ultimately from the normal intake of food and oxygen), which it converts with great efficiency into mechanical work.

The power available from skeletal muscle depends on two factors: the mass of well-vascularised tissue that can be recruited for the purpose and the sustainable power per gram of tissue. Whether one uses a dorsal muscle (such as latissimus dorsi) a ventral muscle (such as rectus abdominis) a muscle from the abdominal cavity (such as psoas major) or a muscle from the lower limb (such as gracilis or vastus lateralis), depends on the way in which power is to be coupled to the circulation. Some configurations require the muscle to be transposed into a new position, diverting it entirely from its normal function; other configurations would allow the muscle to operate in situ. The more indirect the linkage, the more freedom there is in the choice of a suitable muscle, but the poorer the efficiency of utilising the available energy.

For purposes of illustration, let us base our calculations on the generation of energy from a muscle mass of 600 g, which happens to correspond to the average mass of an adult male latissimus dorsi muscle. We are seeking sustainable pumping power of 1·3 W, with a reserve capacity that supports short-term use at up to at least 3 W. The power required of a 600 g muscle would thus correspond to a sustainable 2·1 W/kg of muscle tissue, with the capability of working for shorter periods at 5 W/kg. To what extent is it feasible to expect these levels of work from skeletal muscle, bearing in mind that the human myocardium produces about 4 W/kg at a resting rate?

To answer this question we have used an apparatus designed in our laboratory[16] to characterise the mechanical performance of rabbit tibialis anterior (TA) muscles. From a power-velocity curve, such as that in fig 3, we can obtain the rate of work output (force × velocity) at any velocity of shortening from zero, where the force is maximal but the power is zero, to the maximum unloaded shortening velocity, where all the force produced is used to produce shortening within the muscle, and the external power output is again zero. Between these extremes there is a velocity for which the power output is maximal; this velocity is often referred to as V_{opt}. This curve describes the behaviour of a muscle only in single maximally activated contractions and does not, therefore, give any direct information about the endurance of the muscle. On the other hand, it shows very clearly that the power output of skeletal muscle is highly dependent on the load and that for a muscle to deliver its maximum power it must work against a load that allows it to shorten at a velocity close to V_{opt}.

For an unconditioned rabbit TA muscle, the maximum acute power output is about 300 W/kg. After 8–10 weeks of continuous stimulation at a frequency of 10 Hz, the mass falls to 50% of control and V_{opt} to 25% of control values. The combined effect of these losses is a reduction in power output to about 10% of control values[17 18] (fig 3, lower curve). This looks rather serious until it is recognised that in absolute terms the maximal acute power output of the stimulated muscle is still 30–40 W/kg, close to the systolic power of the left ventricular myocardium. These power outputs refer only to the rate at which work is performed during contraction. In any practical application, the muscle must spend at least as much time in relaxation as in contraction, and since work is available only during contraction the maximum power output is about 20 W/kg. At the specified work rates of 2·1–5 W/kg, then, the stimulated muscle would be working at 10–20% of the maximum. To what extent can such working rates be sustained?

We have conducted fatigue tests on the same rabbit TA muscles under conditions in which they were constrained to perform external work at 10 W/kg. Conditioned muscles were able to maintain this level of work for many hours whereas control muscles showed progressive fatigue at the same initial work rate, even though their maximum power capacity was much greater. Although we have not run such tests at much higher rates of working, we doubt whether such rates could be sustained for more than short periods.

10 W/kg has to be regarded as an overestimate because it is based on rabbit muscle; the specific power of human muscle is intrinsically less, because of its slower contractile characteristics.[19] The difference in power may be less marked when the comparison is made between human and rabbit muscles that are fully conditioned for continuous use, but it would seem sensible to allow for a reduction to 8 W/kg. The actual mass of muscle finally generating work will also be less than the starting mass, for several reasons. First, there is the loss of muscle bulk, already referred to, that is the consequence of performing work continuously at this high level; this stabilises at approximately 50% in the long term.[6] This would reduce the working mass of a muscle such as latissimus dorsi to about 300 g. Second, there is a loss associated with the grafting procedure. The experiments of Guerlinckx *et al*[20] on orthotopic grafting of rabbit rectus femoris muscles suggest that a chronic reduction in mass of 25% would be expected as a result of tendon section alone. This would bring about a further reduction to about 225 g. To this must be added any loss of muscle fibres through ischaemic damage. The power available would therefore be unlikely to exceed 1·8 W.

Recent work from our laboratory suggests that conditioning regimens can be devised that are very much better at preserving muscle mass and contractile speed, and hence the maximum power available in the long term.[21 22] There is less scope for such techniques when the energy demand is continuously high, but they may be useful under partial assist conditions—for example, when only a proportion of the patient's heart beats are assisted.

How may skeletal muscle power be harnessed?

If the power requirements for cardiac assistance (1·3–3 W) are compared with the estimated maximum of 1·8 W available from skeletal muscle, it is immediately clear that, unless a substantially larger muscle mass could be recruited for the task, it is not feasible to attempt total replacement of more than resting heart function in this way. On the other hand, the estimated power available could, if appropriately harnessed, provide a very substantial assist (at an average systemic pressure of 100 mm Hg, 1·8 W is equivalent to more than 8 l/min). What is the best configuration for putting this power to use?

CONFIGURATIONS IN WHICH SKELETAL MUSCLE IS COUPLED DIRECTLY TO THE CIRCULATION

Procedures based on reconfiguration of skeletal muscle alone have considerable advantages over any approach that requires the muscle to be interfaced with non-biological materials (see below). Of these procedures cardiomyoplasty and aortomyoplasty suffer from one serious limitation: the geometry of the pump is dictated by the size and shape of the existing organs. In some ways the consequences of this limitation are obvious: a grossly hypertrophied heart may be too large to be wrapped effectively by the patient's latissimus dorsi muscle; the small lumen of the aorta restricts the stroke volume that can be achieved by compressing it. But just as important as these anatomical considerations are the loading conditions that the fixed geometry imposes on the muscle wrap, because they constrain the muscle to operate far from the peak of its power curve.[17 23] The benefits that have been reported by patients who have had the cardiomyoplasty procedure may be due to the reinforcement given to the myocardial wall, or to the translational motion imparted by contraction of the free portion of the graft.[23]

In contrast, the SMV approach is limited only by the size, shape, and fibre orientation of the latissimus dorsi (or other muscle) that is available. Subject only to these limitations, factors such as cavity volume, wall thickness, and direction of wrap are all within the control of the surgeon and can, given the appropriate basic knowledge, be optimised to provide the maximum pumping performance of which the muscle is capable. Set against this functional potential is the need to ensure that the introduction of such a device into the patient's circulation does not cause thrombus formation, with the attendant risks of obstruction of flow through the device and embolism to vital organs.

CONFIGURATIONS IN WHICH SKELETAL MUSCLE IS COUPLED INDIRECTLY TO THE CIRCULATION

It is possible to envisage several ways in which a skeletal muscle could, in principle, provide the energy for a mechanical assist device, such as a left ventricular assist device (LVAD).

(a) Direct mechanical linkage (fig 2F) would be moderately efficient, especially if the muscle were allowed to operate in its normal line of action and without disturbance to its vascular supply. Problems would be the need for the assist device to be close to the muscle and the difficulty of creating a strong and reliable junction between a muscle and a non-biological surface. The latter is not a trivial matter: even tendon-to-tendon anastomoses take many months to acquire full strength. Furthermore, the junction must be capable of unimpeded translational movement and must remain so.

(b) A hydraulic link could be established by wrapping a muscle around a fluid-filled bladder[24] (fig 2G) or, more conservatively, by arranging for the bladder to divert the muscle from its normal line of action, so that it was compressed when the muscle contracted[25] (fig 2G). This approach would allow a little more freedom in the placement of the assist device relative to the muscle, at the cost of some resistive energy losses in the coupling lines. However, all existing biopolymers are permeable to some extent, so that in the present state of development it would not be possible to avoid a progressive escape of fluid from the system. This problem has yet to be overcome.

(c) An indirect approach (fig 2H), in which contraction of the muscle was coupled to the generation of electricity, has several advantages. It is the most flexible arrangement in terms of placement: for example, an intrathoracic device might be powered by a muscle in the lower limb. There would be a broader choice of assist device, and this could encompass electrically driven devices that had not been designed with skeletal muscle power specifically in mind. However, such an approach poses technological problems that await a reliable solution, and these include the problems of muscle attachment already mentioned.

With an optimistic estimate of 50% efficiency for the energy conversions involved, the maximum pumping power available from human muscle working at 8 W/kg would be 0·9 W, equivalent to 4 l/min for the mechanical and hydraulic approaches. The electromechanical approach involves two conversions, and the maximum pumping power available would therefore be 0·45 W, equivalent to 2 l/min. Thus partial assistance of resting heart function is bordering on feasibility with this technique, but the reserve capacity would be limited.

One of the attractions of this general approach is that it would capitalise on the results of an extensive research effort over several years. For example, devices are already available in which the flow has been well characterised and clinical experience has been accumulated. A major advantage of mechanical devices is that they can provide cardiac assistance as soon as they have been connected to the patient's circulation. Thus in the immediate postoperative period it might be possible to energise the device from an external power source, transferring to endogenous power from muscle after the conditioning process had been completed.

A less obvious advantage of using skeletal muscle as the power source for another device is that it eliminates problems of synchrony with the cardiac cycle. We have already stated that during extreme conditioning the shortening velocity for maximum power, V_{opt}, expressed in fibre lengths per second, declines to about 25% of control values. Apart from the associated power loss, which has already been referred to, the slowing of contraction and relaxation limits the amount of shortening that can take place within one or other phase of the cardiac cycle.[23] Even if the load were optimised to allow the muscle to shorten at V_{opt}, a shortening of 20% would take 400 ms at 0·5 fibre lengths/s. Such considerations become irrelevant if the muscle can be allowed to operate asynchronously.

A major disadvantage of mechanical assist devices is their high cost. This would be increased still further in the case of a device powered by skeletal muscle, which would also require an implantable energy converter and a pacemaker-like neuromuscular stimulator. The long-term success of mechanical circulatory devices is still limited by the biomaterials used in their construction. Materials in current use have a useful life of only about 18 months, but progress in this area has been rapid and this figure could be expected to improve. Reference has already been made to the problems of anchoring the muscle to an artificial device, and the additional problems of leakage associated with a hydraulic system. It is not a trivial anatomical problem to accommodate a mechanical device in the chest when the patient's own heart is still in situ. There is also the problem of finding room for the power converter, although this would be less serious in the case of the electrically driven assist. Finally, all of the existing clinical experience with mechanical circulatory devices has been gained in bridge-to-transplant procedures, and it would be necessary to develop surgical techniques that were not likely to compromise the action of the patient's own heart if such devices were to be used to provide a permanent assist.

Conclusions

When total heart replacement is called for and a transplant is unsuitable or unavailable the mechanical artificial heart is the only option. Mobility, without restraint or encumbrance, should be a major goal of cardiac rehabilitation, so it is appropriate to consider the prospects for implantable devices that are independent of exogenous power sources. We show here that there is little hope of obtaining the energy for such a device entirely from the patient's own skeletal muscle: an electromechanical pump energised in this way would be limited to about 2 l/min, with little in reserve. This is an unsatisfactory outcome for a procedure that is likely to be very expensive. The picture could change if highly efficient energy converters could be harnessed to a much larger muscle mass, but in the present state of development the outlook for this approach is not encouraging. Direct mechanical or hydraulic coupling is potentially more efficient, but requires the assist device to be placed fairly close to the energising muscle. Mechanical and electromechanical approaches pose problems of muscle attachment and the hydraulic approach poses problems of fluid leakage.

Much more power is available if the muscle tissue can be employed directly. With the muscle formed into a pumping chamber and loaded so as to operate around the peak of the power curve, there is sufficient power to produce an average flow as high as 8 l/min. Such an arrangement need not involve mechanical pumps or energy convertors and the hardware cost would therefore be limited to that of an implantable neuromuscular stimulator and, possibly, a valve. The considerable progress that has been made with this type of approach has been the subject of recent reviews.[3 26] Although such configurations could in theory replace the resting function of the left ventricle, a more practical objective would be a partial assist of 1–2 l/min, with the muscle working for much of the time below its maximum capacity. Under these conditions, there would be a better prospect of preserving the contractile speed of the conditioned muscle, with corresponding benefits for the amplitude and duration of each assist cycle and a substantial improvement in the reserve pumping capacity. This, then, is an avenue that could lead to major advances in the surgical treatment of chronic cardiac failure.

We thank the British Heart Foundation and the Science and Engineering Research Council for their support of this work.

1 Salmons S, Henriksson J The adaptive response of skeletal muscle to increased use *Musc Nerve* 1981,4·94–105.
2 Pette D, Vrbová G. Neural control of phenotypic expression in mammalian muscle fibers *Musc Nerve* 1985,8.676–89.
3 Salmons S, Jarvis JC, eds *Harnessing skeletal muscle power for cardiac assistance*. Commission of the European Communities, 1991;ISBN 90-365-0412-0, 123pp.
4 Acker MA, Hammond R, Mannion JD, Salmons S, Stephenson LW. An autologous biologic pump motor. *J Thorac Cardiovasc Surg* 1986;12:733–46.
5 Clark BJ III, Acker MA, McCully K, Subramanian HV, Hammond RL, Salmons S, *et al* In vivo ^{31}P-NMR spectroscopy of chronically stimulated canine skeletal muscle *Am J Physiol* 1988;254·C258–66
6 Mayne C, Anderson WA, Hammond RL, Eisenberg BR, Stephenson LW, Salmons S Correlates of fatigue resistance in canine skeletal muscle stimulated electrically for up to one year. *Am J Physiol· Cell Physiol* 1991;261 *(Cell Physiol* 30*)*:C259–70
7 Chagas ACP, Moreira LFP, da Luz PL, Camarano GP, Leirner A, Stolf NAG, *et al* Stimulated preconditioned skeletal muscle cardiomyoplasty An effective means of cardiac assist *Circulation* 1989;80 (Suppl III).202–8.
8 Hagege AA, Desnos M, Chachques J-C, Carpentier A, Fernandez F, Fontaliran F, *et al* Preliminary report· follow-up after dynamic cardiomyoplasty *Lancet* 1990; 335:1122–4.
9 Pattison CW, Cumming DVE, Williamson A, Clayton-Jones DG, Dunn MJ, Goldspink G, Yacoub M. Aortic counterpulsation for up to 28 days with autologous latissimus dorsi in sheep. *J Thorac Cardiovasc Surg* 1991, 102·766–73
10 Kochamba G, Desrosiers C, Dewar M, Chiu R-C. The muscle-powered dual-chamber counterpulsator rheologically superior implantable cardiac assist device. *Ann Thorac Surg* 1988,45 620–5
11 Anderson DR, Pochettino A, Hammond RL, Hohenhause E, Spanta AD, Bridges CR Jr, *et al.* Autogenously lined skeletal muscle ventricles in circulation Up to nine months' experience *J Thorac Cardiovasc Surg* 1991, 101 661–70
12 Pochettino A, Anderson DR, Hammond RL, Salmons S, Stephenson LW. Skeletal muscle ventricles. *Seminars Thorac Cardiovasc Surg* 1991,3:154–9.
13 Frey M, Thoma H, Gruber H, Stohr H, Havel M The chronically stimulated psoas muscle as an energy source for artificial organs an experimental study in sheep. In Chiu RC-J, ed *Biomechanical cardiac assist. Cardiomyoplasty and muscle-powered devices.* Mount Kisco, New York Futura Publishing Company, 1986·179–91.
14 Ugolini F Skeletal muscle for artificial heart drive. theory and in vivo experiments In Chiu RC-J, ed. *Biomechanical cardiac assist Cardiomyoplasty and muscle-powered devices.* Mount Kisco, New York: Futura Publishing Company, 1986:193–210
15 Hurst JW, ed. The heart, arteries and veins. New York· McGraw-Hill Book Company, 4th ed, 1978·76
16 Jarvis JC, Salmons S. An electrohydraulic apparatus for the measurement of static and dynamic properties of rabbit muscles. *J Appl Physiol* 1991;70:938–41
17 Salmons S, Jarvis JC. Cardiomyoplasty: the basic issues *Cardiac Chron* 1990,4.1–7
18 Salmons S, Jarvis JC. The working capacity of skeletal muscle transformed for use in a cardiac assist role In: Chiu RC-J, Bourgeois IM, eds *Transformed Muscle for Cardiac Assist and Repair*. Mount Kisco, NY. Futura Publishing Company, 1990 89–104
19 Faulkner JA, Claflin DR, Brooks SV, Burton HW Power output of fiber segments from human latissimus dorsi muscles· implications for heart assist devices In· Carraro U, Salmons S, eds. *Basic and Applied Myology· Perspectives for the 90's*. Padua: Unipress, 1992·31–8.
20 Guerlinckx PJ, Faulkner JA, Essig DA. Neurovascular-anastomosed muscle grafts in rabbits: functional deficits result from tendon repair *Musc Nerve* 1988,11 745–51.
21 Jarvis JC, Mayne CN, Little P, Sutherland H, Brownson C, Salmons S Use of 2 5 Hz and 10 Hz stimulation to examine coordination in the phenotypic response of fast skeletal muscle to increased use. *Musc Res Cell Motil* 1991,13.237.
22 Jarvis JC, Mayne CN, Salmons S Basic studies on skeletal muscle for cardiac assistance. *J Cardiac Surg* 1991,6 (suppl).204–9
23 Salmons S, Jarvis JC. Cardiomyoplasty a look at the fundamentals In Carpentier A, Chachques J-C, Grandjean P, eds. *Cardiomyoplasty* Mount Kisco, NY Futura Publishing Company, 1991.3–17.
24 Anderson WA, Bridges CR, Chin AJ, Andersen JS, Acker MA, Hammond RL, *et al.* Long-term neurostimulation of skeletal muscle. its potential for a tether-free biologic cardiac assist device. *PACE* 1988,11:2128–34.
25 Li CM, Hill A, Colson M, Desrosiers C, Chiu RC-J Implantable rate-responsive counterpulsation assist system. *Ann Thorac Surg* 1990;49 356–62.
26 Hooper TL, Stephenson LW. Using skeletal muscle to assist the heart. *Br Heart J* 1991,66:261–3.

Br Heart J 1992;68:339–41

BRITISH CARDIAC SOCIETY

Surgical cover for percutaneous transluminal coronary angioplasty

The Council of the British Cardiovascular Intervention Society

Members of the Council of the British Cardiovascular Intervention Society:
P J Hubner
R Balcon
J Dyet
D S Dymond
H H Gray
R J Hall
M M Khan
A F Mackintosh
M T Rothman
T R Shaw
M F Shiu
R P Wilde

Correspondence to:
Dr P J B Hubner,
Department of Cardiology,
Groby Road Hospital, Groby
Road, Leicester LE3 9QE.

Accepted for publication
15 January 1992

Surgical cover for coronary angioplasty can be an emotive subject. All who practise percutaneous transluminal coronary angioplasty or provide emergency surgical cover are concerned that the procedure should be performed as safely as possible. To this end many consider that it is essential to have surgical facilities at the same hospital—so-called on site surgery—so that if a vessel occludes during percutaneous transluminal coronary angioplasty, emergency coronary artery bypass grafting can be promptly effected. Some consider that there may be insufficient time for a patient to travel from one hospital to another in an ambulance to have emergency surgery. In 1990 Parker expressed the view that "It is more appropriate for the cardiologist to travel by car than for patients with acute myocardial ischaemia (who perhaps will require cardiopulmonary resuscitation) to travel by ambulance".[1]

The joint recommendations of the American College of Cardiology and the American Heart Association are that on site surgical cover is essential for percutaneous transluminal coronary angioplasty.[2] In France and Germany large numbers of percutaneous transluminal coronary angioplasties are done without on site cover.[3] This topic was initially brought to the British Cardiovascular Intervention Society to consider the safety and medico-legal status of centres in the United Kingdom performing percutaneous transluminal coronary angioplasty without surgical cover on site.

Need for emergency cardiac surgery for percutaneous transluminal coronary angioplasty

With increased experience and improved equipment the need for emergency surgery has fallen considerably. In the United States the National Heart, Lung and Blood Institute Registry recorded that the rate for emergency surgery during percutaneous coronary angioplasty fell from 5·8% between 1979 and 1981 to 3·4% in 1985.[4] In the United Kingdom Shiu *et al* reported an emergency surgery rate of 6·6% for cases between 1983 and 1985.[5] In 1989 from all United Kingdom centres the British Cardiovascular Intervention Society recorded an emergency surgery rate of 2·1%.[6] From 63 American centres in 1990 the emergency surgical rate was 1·6%.[7]

The transfer of a patient to a theatre while being given external cardiac massage is now rarely required. With current experience, techniques, and devices, it is usually possible at least partly to re-establish blood flow if a vessel does occlude. The vessel may already have a guide wire across the dissected region, or it may be possible to re-cross the occlusion. A Stack or another perfusion balloon may restore flow. Stents are becoming more readily available as bail-out devices. The circulation can be supported by an intra-aortic balloon pump or by a cardiopulmonary support system. For high risk cases these support systems can be established before the start of coronary angioplasty. In at least half the cases in which the vessel becomes occluded it is possible to re-establish adequate flow with modern devices without the need for emergency coronary artery bypass surgery.[8,9] If surgery is needed, it is usual for the patient to be haemodynamically stable and immediate or instant surgery is rarely needed.

On site cardiac surgery

Having surgical facilities on site may not necessarily guarantee immediate or even prompt surgery. There may be no theatre available nor a surgical team. Except for high risk cases many, if not most, centres in the United Kingdom performing percutaneous transluminal coronary angioplasty do so without a free theatre and a surgical team standing by. Because the risk of needing these facilities is approximately 2%, or less in some centres, it is uneconomic to have these facilities left idle. Many centres arrange percutaneous transluminal coronary angioplasty to coincide with the end of one surgical case and before the start of the next. This arrangement can fail if a complication develops in the late stages of the first surgical operation or if the patient having percutaneous transluminal coronary angioplasty develops late vessel occlusion after the start of the second surgical operation. Some centres with on site surgery do not have surgical facilities in the same building. Hence the availability of surgical cover provided by units with on site surgery may be quite variable.

It is quite possible that a centre with off site surgical facilities but with a well thought out and effective plan for transferring a patient to an operating theatre in a surgical centre may

Percutaneous transluminal coronary angioplasty in the United Kingdom 1989 and 1990: comparison between centres with on site and off site surgical facilities

	On site		*Off site*	
Data	*1989*	*1990*	*1989*	*1990*
Centres	45	45	6	6
Numbers	6146	7878	425	581
Mortality	40 of 6146 (0·65%)	56 of 7259 (0·77%)	3 of 425 (0·71%)	0 of 581
Emergency coronary artery bypass surgery	130 of 6146 (2·1%)	161 of 7259 (2·2%)	6 of 425 (1·4%)	6 of 559 (1·1%)
Myocardial infarction	116 of 4861 (2·4%)	115 of 6139 (1·9%)	6 of 425 (1·4%)	13 of 559 (2·3%)

be able to match the time to revascularisation that can be achieved with well organised on site surgery.[10] Reviewing the subject of surgical cover for the British Cardiovascular Intervention Society, a barrister wrote "It is recognised that the key to effective surgical cover, whether on site or off is the rapid transfer of the patient and the prompt availability of theatre and surgical staff ".

Results from the United Kingdom centres with off site surgery

The British Cardiovascular Intervention Society in the 1989 and 1990 audits of interventional procedures in the United Kingdom assessed the results from the six centres performing coronary angioplasty without surgery on site.[6 11] The mortality for percutaneous transluminal coronary angioplasty from these centres was not significantly different from that in centres with surgery on site. The need for emergency coronary artery bypass surgery was less for centres with off site surgery and this was not at the expense of more myocardial infarctions (table). It is accepted that the cases from the two types of centre were not identical and that only a controlled trial could fully assess the results from the two types of centre. The important fact, however, is that with case selection, appropriate techniques, and transport arrangements there was not a significantly higher mortality or other complications with surgery off site.

Case selection of patients having percutaneous transluminal coronary angioplasty with off site surgery

Shaw in the United Kingdom[12] and Morice in France[13] showed that a wide range of cases can be dilated safely without on site surgery. While a high risk case can be identified it is more difficult to predict the haemodynamic consequence of vessel occlusion in a low risk case—for example, a single vessel percutaneous transluminal coronary angioplasty in single vessel disease. Hence a low risk patient may need prompt surgery as much as one predicted to be of high risk. The operator should choose, in the light of his or her experience and available facilities, which cases should be attempted.

Training for percutaneous transluminal coronary angioplasty

If case selection does not need to be determined solely by the presence or absence of surgical facilities on site, nor should training for percutaneous transluminal coronary angioplasty be restricted to centres with on site surgical facilities. The number, variety and complexity of procedures are the relevant features for training. Training for percutaneous transluminal coronary angioplasty at centres with on or off site surgical facilities is discussed in greater detail in the paper from the Council of the British Cardiovascular Intervention Society on Training for Percutaneous Transluminal Coronary Angioplasty.[14]

On site cardiac surgery the strongly preferred option

While percutaneous transluminal coronary angioplasty can be done safely with off site surgery, the need to transport a patient to another hospital complicates the procedure. This is why the British Cardiovascular Intervention Society considers that **on site surgery is the strongly preferred option.** For a new centre starting up percutaneous transluminal coronary angioplasty the British Cardiovascular Intervention Society recommends that on site surgery is to be strongly preferred. The British Cardiovascular Intervention Society does, however, support those centres that perform percutaneous transluminal coronary angioplasty with surgery off site and considers that it is both safe and ethical, provided that reliable arrangements to allow prompt transfer to a theatre and surgeon are in place. These views are similar to those expressed in two recent reports which discussed surgical cover for angioplasty, namely the Report of a Working Party of the British Cardiac Society on Coronary Angioplasty in the United Kingdom[3] and the Fourth Joint Report of the Provision of Services for the Diagnosis and Treatment of Heart Disease.[15]

Length of time to revascularisation

The sooner revascularisation can be performed after a vessel occlusion the better and the less ischaemic damage will result. However, to give an upper maximal time limit is not appropriate because this will depend on the haemodynamic state of the patient and will also vary with the time spent in the catheter room while attempts are made to re-open the artery.

Other safety factors relevant to percutaneous transluminal coronary angioplasty

The availability of surgical cover for percutaneous transluminal coronary angioplasty though an important safety factor is not the only one. The quality of the *x* ray equipment can greatly influence the assessment of the procedure and results of percutaneous transluminal coronary angioplasty. The experience of the operator and the whole catheter room team—that is, nurse, physiological measurement technician, and radiographer—has an important influence on the safety of percutaneous transluminal coronary angioplasty.

Newer interventional procedures

Surgical cover for percutaneous transluminal coronary angioplasty has mainly been considered for dilatation procedures with a balloon. With balloon dilatation vessel perforation is rare. With debulking procedures (such as atherectomy, lasers, and drills) as well as the risk of vessel occlusion there is the additional risk of vessel perforation and possible cardiac tamponade.[16-18] Some devices are relatively rigid and may require larger than usual guide catheters; these features lead to the risk of vessel wall damage and occlusion at a site away from the target lesion.[18] Many operators practising debulking procedures are still on the learning curve of their experience with these relatively new devices. For these reasons particular care over surgical cover should be taken for patients in whom debulking devices are to be used.

Recommendations of the British Cardiovascular Intervention Society on surgical cover for percutaneous transluminal coronary angioplasty

The topic of surgical cover for percutaneous transluminal coronary angioplasty has been discussed by the Council of the British Cardiovascular Intervention Society and at the scientific meetings of the society. Opinions have been obtained from a barrister and from a physician specialising in medico-legal subjects. As a result of all these discussions the British Cardiovascular Intervention Society makes the following recommendations about surgical cover for percutaneous transluminal coronary angioplasty:

1 The aim of surgical cover for percutaneous transluminal coronary angioplasty is to provide re-vascularisation after vessel occlusion and to treat other complications such as vessel perforation. To enable emergency surgery to be performed as quickly as possible **on site surgery is the strongly preferred option.**

2 It is recognised that percutaneous transluminal coronary angioplasty can be performed properly and safely without on site surgery with results that are comparable to those for units that have surgical facilities on site.

For units without surgery on site reliable arrangements to allow prompt transfer of the patient to a suitable operating theatre and surgeon are essential. Transfer should be in an ambulance with staff and equipment to allow for cardiac resuscitation and support.

3 There should be a close and regular liaison between cardiologists and radiologists performing percutaneous transluminal coronary angioplasty and the cardiac surgeons to whom a patient may need to be transferred in an emergency.

4 It is recognised that the key to effective surgical cover, whether on site or off, is the rapid transfer of the patient and the prompt availability of theatre and surgical staff.

The British Cardiovascular Intervention Society considers that these recommendations may need modification in the light of further experience in the practice of percutaneous transluminal coronary angioplasty.

1 Parker DJ Does angioplasty need on site surgical cover? A surgeon's view. *Br Heart J* 1990,64 1–2
2 A report of the American College of Cardiology/American Heart Association Task Force on assessment of diagnostic and therapeutic cardiovascular procedures (sub committee on percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 1988;12.529–45.
3 Coronary angioplasty in the United Kingdom. Report of a working party of the British Cardiac Society. *Br Heart J* 1991;66.325–31
4 Detre K, Holubkov PHR, Kelsey S, *et al.* Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981. The National Heart, Lung and Blood Institute Registry. *N Engl J Med* 1988;318 265–70
5 Shiu MF, Silverton NP, Oakley D, Cumberland D. Acute coronary occlusion during percutaneous transluminal coronary angioplasty. *Br Heart J* 1985,54 129–33
6 Hubner PJB on behalf of the British Cardiovascular Intervention Society. Cardiac interventional procedures in the United Kingdom during 1989 *Br Heart J* 1991, 66 469–71.
7 Noto TJ, Johnson LW, Krone R, *et al* Cardiac catheterization 1990: A Report of the Registry of the Society for Cardiac Angiography and Interventions (SCA & I). *Cathet Cardiovasc Diagn* 1991,24.75–83.
8 Cripps TR, Morgan JM, Rickards AF Outcome of extensive coronary artery dissection during coronary angioplasty. *Br Heart J* 1991;66 3–6.
9 Landau C, Jacobs AK, Currier JW, *et al.* One year follow up of PTCA induced dissections treated with a perfusion balloon catheter. *Circulation* 1991;84 (suppl. II):131
10 Levy RD, Bennett DH, Brooks NH. Desirability of immediate surgical standby for coronary angioplasty. *Br Heart J* 1991,65:68–71
11 Hubner PJB. Cardiac Interventional Procedures in the United Kingdom during 1990 A British Cardiovascular Intervention Society report. *Br Heart J* (in press)
12 Shaw TRD. Does angioplasty need on site cover? A physician's view *Br Heart J* 1990,64·3–4.
13 Morice MC, Bourdin Ph, Glatt B, *et al.* 1005 coronary angioplasties without local surgical standby and patients' management in failed procedure [abstract]. *Eur Heart J* 1989,10 187.
14 Gray HH, *et al.* Guidelines for training in percutaneous transluminal coronary angioplasty (PTCA). Document from the Council of the British Cardiovascular Intervention Society. *Br Heart J* (In press).
15 Provision of Services for the diagnosis and treatment of heart disease. Fourth Report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England. *Br Heart J* 1992,67:106–16.
16 Vlietstra RE, Abbotsmith CW, Douglas JS, *et al* Complications with directional coronary atherectomy Experience at eight centres [abstract] *Circulation* 1989;80(suppl II) 582.
17 Geschwind HJ, Zelinsky R, Dubois-Rande JL. Pulsed mid-infrared coronary laser angioplasty: initial results [abstract]. *Eur Heart J* 1991;12:98.
18 Hinohara T, Rowe MH, Robertson GC, Selmon MR, Braden L, Leggett JH, Vetter JW, Simpson JB. Effect of Lesion Characteristics on Outcome of Directional Coronary Atherectomy. *J Am Coll Cardiol* 1991,17 1112–20.

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words*
- *In general, no letter should contain more than six references (also typed with double spacing)*

Effect of early intravenous heparin on coronary patency infarct size, and bleeding complications after alteplase thrombolysis

SIR,—In the interpretation of the results of a clinical trial where the null hypothesis has been rejected, it is important to discern whether any systematic biases, especially if unbalanced between treatment groups (confounders), could (partially) explain the results. The European Cooperative Study Group (*British Heart Journal* 1992;67:122–28) contended that early concomitant intravenous heparin therapy improves coronary patency at 48–120 hours in patients treated with alteplase.[1] The difference although small (83% heparin, 74% placebo) was deemed statistically significant. However, fewer patients in the heparin group (83%) showed enzymatic evidence of infarction than in the controls (95%). Indeed, although this difference is larger than that of the patency benefit, conventional statistical significance was apparently not achieved. Using the same statistical technique, I estimate that the relative risk of not sustaining an enzymatic infarction in the placebo group compared with the heparin group was 0 31 (95% CI 0 18 to 0·52), clearly significant.[2]

Moreover, one might assume that coronary vessels in the non-infarction patients would be patent If included, they would tend to bias the results in favour of patency benefit with heparin. If you eliminate these patients from table 2 (55 heparin, 17 control) and assume that they also account for the 24 subjects where the infarct related vessel could not be identified (nine heparin, 15 control), the results are very different, less marked and may be due to the play of chance (for TIMI grade 0 or 1 perfusion: heparin 20·1% *v* placebo 25·5%; relative risk 0·79, 95% CI 0·56 to 1·11).

While analysis based on the intention-to-treat principle is regarded as the method most likely to minimise bias, including patients without the disease of interest seems inefficient and may limit the internal and external validity of the conclusions. This may be more of an issue in explanatory or "efficacy" trials, such as this one, than in pragmatic or "effectiveness" trials.[3]

I argue that when an adequate dose of aspirin is administered, intravenous heparin has little (if any) effect on coronary patency at 48–120 hours in patients treated with alteplase

DAVID R MASSEL
Cardiac Care Unit,
Victoria Hospital,
London, Ontario,
Canada

1 de Bono DP, Simoons ML, Tijssen J, *et al.* Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis. results of a randomised double blind European Cooperative Study Group trial. *Br Heart J* 1992,67·122–8.
2 Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised mortality rates. *Br Med J* 1988;296·1313–6
3 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chron Dis* 1967,20.637–48

This letter was shown to the authors who reply as follows.

SIR,—Dr Massel takes us to task for not confining our comparison of alteplase heparin with alteplase plus placebo to patients with confirmed myocardial infarction. Clearly, it is impossible to be sure that the diagnosis of infarction will be confirmed at the time of trial entry. The difficulty of confining the analysis to patients with a retrospectively confirmed infarct is that it is well known and documented that early effective thrombolytic therapy will prevent the development of Q waves and/or a diagnostic increase in plasma enzyme concentration in a proportion of patients with genuine thrombotic coronary occlusion. To confine analysis to those patients subsequently shown to have infarction would be to introduce an entirely arbitary bias against whatever in fact was the most effective treatment. The conventional approach in trials of this nature is to enter the patients on the basis of clinical and electrocardiographic criteria (and those we adopted were stringent compared with several other trials) and then to analyse on an intention-to-treat basis.

It could be argued that the reduction in cases of confirmed infarction among the group receiving heparin was indeed a consequence of earlier and better sustained patency in the heparin treated group. However, since this was not one of the a priori end points we refrained from attaching weight to this in our discussion.

DAVID DE BONO
Department of Cardiology,
University of Leicester
Clinical Science Wing,
Glenfield General Hospital,
Leicester LE3 9QP

Incessant atrial tachycardia accelerated by pregnancy

SIR,—Dr Doig and colleagues[1] described their experience with a patient in whom incessant atrial tachycardia developed during pregnancy (*British Heart Journal* 1992; 67:266–8). We have recently seen a similar case and feel that certain observations may be pertinent.

A 34 year old woman was admitted at 38 weeks' gestation with palpitation. This had been present for five days and was noticeable only at rest. She was otherwise well and denied previous symptoms. She was in her fourth pregnancy; the third had required a caesarean section for placenta praevia. On admission her pulse rate was 200 per minute and her blood pressure was 90/70 mm Hg.

The electrocardiogram showed a narrow QRS complex tachycardia with upright P waves in V1 and a frontal P wave axis of +10°. The PR interval was 160 ms and the RP interval was 200 ms. The electrocardiogram was therefore consistent with atrial tachycardia and 1:1 ventricular conduction Intravenous verapamil (10 mg) had no effect on the ventricular rate and two hours later she was given disopyramide (150 mg). This caused her blood pressure to fall to 70/50 mm Hg but did not improve the ventricular rate. She therefore underwent elective cardioversion, which also proved unsuccessful despite two shocks of 360 J delivered via standard paddle positions. Her atrial tachycardia showed considerable diurnal variation with pulse rates ranging from 135 when asleep to 215 per minute when awake and being examined. The results of fetal heart monitoring remained normal throughout this period and fetal movements were maintained. Intravenous flecainide succeeded in slowing the atrial rate to 130 per minute and precordial echocardiography showed a dilated left ventricle and impaired left ventricular function. In view of her advanced gestation she underwent elective caesarean section and gave birth to a live female weighing 3180 g who had an Apgar score of 7 at one minute and 10 after five minutes.

After delivery she remained in an atrial tachycardia but during the next week her pulse rate fell progressively and her blood pressure rose. At the time of discharge her pulse rate was 100 beats per minute at rest. At auscultation a murmur of mitral regurgitation and a loud third heart sound were heard. Between three and eight weeks after delivery she reverted to sinus rhythm and the P wave configuration showed a prominent left atrial component. There was T wave inversion in all the precordial leads Two months after delivery left ventricular function remained mildly impaired. Although these changes may have been seconary to the dysrhythmia, their persistence suggests an underlying cardiomyopathy.

Our own experience accords with that of Doig *et al* The considerable fluctuations in rate and resistance to both pharmacological and electrical cardioversion are in keeping with an automatic atrial tachycardia. In view of the catecholamine drive (as shown by these fluctuations) we considered β adrenocepter blockade, but her low blood pressure and impaired left ventricular function precluded this treatment. Late in pregnancy standard paddle positions for cardioversion are difficult to obtain and antero-posterior positioning of the paddles might have helped. Delivery of the baby was followed by progressive resolution of the tachycardia and when the fetal lung is likely to be mature this is perhaps the best treatment for both mother and child. Finally, despite its fast rate, the arrhythmia was remarkably well tolerated whereas antiarrhythmic drug treatment caused a considerable fall in blood pressure.

JEREMY J MURPHY
DAVID J R HUTCHON
Department of Medicine,
Memorial Hospital,
Darlington,
County Durham DL3 6HX

1 Doig JC, McComb JM, Reid DS. Incessant atrial tachycardia accelerated by pregnancy. *Br Heart J* 1992,67 266–8.

Br Heart J 1992;68:343–4

BRITISH CARDIAC SOCIETY NEWSLETTER

Changes within the Society

We are near the completion of the planned restructuring of the Society. In the past two years a system of committees was set up, a closer liaison was developed with the affiliated groups, a wider range of activities was adopted, and the new premises were purchased. We have now made an important new appointment. Patrick Fagan, CB, MBE will take up duties as executive officer of the Society from 1 September. Until recently, Patrick Fagan was Director General of Military Survey (as a Major General) with responsibilities to the Chiefs of the three armed services in relation to all forms of geographical information needed for maps, charts, and intelligence world wide. He directed a staff of 1500, of which 1000 were civilian. He is a London graduate (MSc) with diplomas in civil engineering, surveying, and photogrammetry. Patrick Fagan is a Fellow of the Royal Institution of Chartered Surveyors and a Fellow of the British Institute of Management. His wide interests are reflected in other activities. He is Vice President of the Royal Geographical Society, Chairman of the Mount Everest Foundation, and holds appointments relating to mountain sports and rugby. He has extensive international experience, and may be familiar to members because of frequent television appearances during the Gulf War. We welcome him to the Society and we are delighted with the new strengths that he will bring.

While we welcome one new colleague we are saddened to lose another. Elaine Brown, who has been our Administrator for five years, has decided to take the opportunity presented by the restructuring to seek new challenges. Elaine has contributed a great deal: her concerns for the Society and her loyalty to it have been a source of strength to us. With Jenny Lodge she has borne the heat of the day during the demanding organisational evolution and the physical moves of the Society. Her decision has therefore been a disappointment. We wish her well. We know that her interests in the well-being of the Society continue, and we hope that links will remain after she leaves at the end of July—several weeks before this newsletter appears.

Björk-Shiley valves

We mentioned the problem of strut fractures in some types of Björk-Shiley valves in our newsletters of March 1991 and February 1992. We regretted the anxiety for patients with valve replacements caused by the continuing publicity—though we accepted it was inevitable—and we discussed the MedicAlert proposals. Few then considered that elective replacement would be warranted. But the situation has continued to evolve as more information becomes available. The recent Dutch follow up study of 2303 patients published in February (*Lancet* 1992;332:257–61) raised the level of concern particularly for the 70°CC mitral valves that had a cumulative risk of outlet strut fracture of 17·4% over eight years. Younger patients were also at greater risk. Elective replacement was recommended by the authors for selected groups of patients with both 60° and 70° valves, but—mindful of the operative mortality—few units in the United Kingdom have adopted this policy so far. Confirmation (or otherwise) of the Dutch data became an urgent priority Shiley have now released information that has been sent to all doctors in the United Kingdom based on re-analysis of their database with new definitions of risk groups particularly focusing on weld dates. The groups at highest risk (60°CC) show estimated annual fracture rates for size 33 mitral valves as follows: 2·52% for welds 1 July 1981 to 30 June 1982, 1·46% for welds 1 January to 30 June 1981, 1·08% for welds before 1 January 1980, and 1·08% for welds from 1 July 1982 to 31 March 1984. In addition, the size 31 mitral valves have an estimated fracture rate of 1·24% for welds from 1 July 1981 to 30 June 1982. The information, perhaps with slight update modifications, should be known to all cardiac surgeons and cardiologists well before this newsletter appears, and may also by then have been supplemented by data specific to the United Kingdom. Difficult decisions will have to be made. Two factors, however, should be borne in mind. First, the data are almost certainly an underestimate, since many patients with prosthetic valves die without recent expert review and without necropsy. Secondly, the often quoted average operative mortality figure for "re-do" mitral replacement of 10% is based upon series with severe complications such as endocarditis, valve dehiscence, and valve clot with complicating heart failure. We have no good data as yet for elective re-operation but mortality will be appreciably lower. We are aware from discussions with colleagues that many cardiac surgeons now accept the need for intervention in some patients. For those with the most vulnerable valves the risk of re-operation may be little or no greater than the risk of a fatal fracture within only two years. Cardiologists and surgeons will be keeping the matter under the closest review as more data, and more specific United Kingdom data, become available. (Early information suggests the failure rate in the United Kingdom may be lower than the overall figures, but the possibility of under-reporting is a concern.)

We have no available evidence that non-invasive tests can detect an early risk of valve failure, though there would be a great advantage to both patients and their professional advisers if one could be developed. Shiley has an active research programme in animals—and we know that progress is being made—based on sophisticated signal processing of relatively simple acoustic measurements and sophisticated radiographic techniques. Even if tests can be devised that have (alone or in combination) acceptable sensitivity and specificity we still face one major problem. Only one third of the CC valves inserted in the United Kingdom have been traced so far. Thus many patients may be unaware that they face potential risk. This problem is also being addressed vigorously through several different avenues of enquiry and the situation will doubtless improve.

Fenfluramine and primary pulmonary hypertension

Celia Oakley has written for the newsletter a follow up on this topic. "Events have moved on since the announcement at Harrogate of a survey of the possible association between fenfluramine and the development of primary pulmonary hypertension. I asked for retrospective information (rather like yellow card reporting) in order to get some idea of the likely numbers and would still like to have this information from colleagues. I am pleased to announce the establishment of an international prospective case control study on this matter. Cardiologists will be asked only to let me know by telephone of all newly diagnosed cases of primary pulmonary hypertension, whether or not there was any association with fenfluramine They will then be asked to allow a visiting research registrar to examine the data, and to permit a trained interviewer to talk to the patient as well as to four control patients drawn from the patient's general practice. Permission will of course be sought from the general practitioner. This is an advance notice. Letters with further details will be sent to all members of the Society. The study has the blessing of the Committee on Safety of Medicines. The coordinating centre is at McGill University in Canada. In summary, all that is required of cardiologists is one telephone call to Celia Oakley on 081 740 3141."

Training programme

Arrangements for the new three-plus-three specialty trained programmes are progressing, and have started or been planned in detail in several Regions. We hope soon to report the results of discussions on the general medical component of the specialist programmes, but Brian Pentecost—as Medical Coordinator—has said that the Joint Committee on Higher Medical Training (JCHMT) is now prepared to look at all submitted training programmes in cardiovascular medicine for the first three year period. The individual limbs of a three year rotational programme cannot be viewed independently, but the JCHMT will make judgements on the complete three year programme. These will eventually be inspected together with the second (senior registrar) post within the same Region or cardiac centre. In the meantime, cardiologists who are planning for the new structure of training should submit details of agreed rotations to the JCHMT office. Many will have already done this when the new plans were first discussed, but no action will be taken by JCHMT unless up to date submissions are made.

Training log books

Members of the Society will have received in the last mailshot an application form for the British Cardiac Society Log Book for invasive and interventional procedures These have been produced by the British Cardiovascular Intervention Society in association with the British Paediatric Cardiology Association and the British Pacing and Electrophysiology Group. Huon Gray has written for the newsletter: "It is directed mainly to those in training. The book allows brief details to be entered on all cases undergoing diagnostic cardiac catheterisation, interventional procedures, pacing, and electrophysiology. This should provide an excellent personal record for those training in the cardiac catheter laboratory, and trainees are encouraged to apply for their own copy. As many, if not the majority, of trainees who will require the log book will not yet be members of the Society, it would be helpful if the application forms were circulated within cardiac departments to all registrars who might be interested in obtaining one. The application forms are also available from the British Cardiac Society, which has funded the project."

Royal Medical Benevolent Fund

Members who attended the Harrogate meeting will have seen the display stand for the Royal Medical Benevolent Fund (24 King's Road, Wimbledon, London SW19 8QN. Tel: 081 540 9194). Perhaps few—other than senior members from St George's—will have recognised Mrs Judith Leatham who is a devoted member of the fund and who was on the stand for much of the time. There was also enthusiastic participation by the local guild of the Royal Medical Benevolent Fund. We have had a letter of thanks from the chairman, Dr JW Brooke Barnett. He wrote "Many doctors are unaware of the existence of the professions's leading charity which helps nearly 700 doctors and their dependants each year. It was, therefore, very fortunate that for the first time the British Cardiac Society at its annual meeting in Harrogate this year allowed the Royal Medical Benevolent Fund to be represented. The distribution of grants to doctors and their families in distress exceeds the income from the traditional means of collecting money for charities by covenants, subscriptions, and fund raising activities." A large number of members and guests requested information, and we hope they will continue to support a charity that is very much our own.

News from Europe

Philip Poole-Wilson is writing a series of short articles to increase our familiarity with the European Society of Cardiology. "To some members of the British Cardiac Society, the European Society of Cardiology may appear as a large, distant, and amorphous body. That image partly arises because of the size of the Annual Congress which is the major annual event organised by the Society, and partly because its activities may not be well known. A newsletter is being sent to all members of the European Society of Cardiology in an endeavour to improve communications and make members aware of developments in European cardiology. We hope that it will be sent twice each year. By now the first one has probably arrived.

The 1991 Congress in Amsterdam attracted 13 151 registered persons of whom 9308 were active participants from 76 countries. The numbers have increased steadily over the last few years. The size presents enormous difficulties to the organisers. Only a few places in Europe can provide sufficient lecture theatres, exhibition space, and hotels The aim is to have the congress in the last two weeks of September. That has proved difficult, but the board is aware of problems with holidays and schooling. In 1996, the annual Congress will take place in Birmingham (August 25 to 29). If that is a success Birmingham may become a regular site for future meetings into the next century.

The European Society of Cardiology is made up of 32 national societies and 24 working groups. Anyone who is a member of the national societies is also a member of the European Society of Cardiology. A few additional persons are members of the European Society of Cardiology through the working groups. That arrangement particularly applies to non-medically qualified persons and scientists. The total membership is now more than 16 000. The population covered by the cardiologists who are members is in excess of half a billion. Although there is complete intermingling of functions amongst cardiologists, in broad terms the national societies represent the profession and the working groups represent cardiologists and scientists with an interest in a particular facet of cardiology. The working groups are: exercise physiology, epidemiology, pathophysiology, valvular heart disease, drug therapy, computers in cardiology, myocardial function, peripheral circulation, nuclear cardiology, anatomy and pathology, microcirculation, thrombosis, echocardiography, rehabilitation, arrhythmias, hypertension, cardiac pacing, myocardial and pericardial disease, coronary circulation, grown-up congenital heart disease, electrophysiology, atherosclerosis, pulmonary circulation, and cardiovascular nursing.

If you wish to become a member of these working groups (and you are encouraged to do so) please write to the appropriate chairman. The names and addresses can be found in the pink pages at the back of the *European Heart Journal*." More from Europe next month . .

News of colleagues

Appointments recently (subject to the usual ratification) have included Thomas Marwick as senior lecturer and honorary consultant at St Mary's Hospital Medical School and John Morgan as consultant cardiologist at Southampton General Hospital. For the single quarter from January to March 1992 a total of nine appointments were made in cardiology in England and Wales—more than in any other medical specialty. 1992 was expected to be a bleak year for new consultant appointments, because only two retirements were planned. We hope that new posts will continue to be created, but there seems little prospect of avoiding a dearth of fully trained senior registrars over the next few years.

News of meetings

Steven Walton, chairman of the British Nuclear Cardiology Group, has asked us to give notice of a one day symposium on "The Assessment of Myocardial Viability that will be held on 18 September 1992 at St Thomas' Hospital. The programmed sections and speakers are as follows· biochemistry (Dr P Garlick, UMDS: electrocardiography (David Mulcahy, Royal Brompton); rest-stress echocardiography (John Chambers, UMDS); nuclear medicine (Professor J McKillop, Glasgow); MRI/CT (Dr D Pennell, Royal Brompton), and PET Scanning (Professor J Melin, Louvain). Further details may be obtained from Dr T Nunn, Department of Nuclear Medicine, St Thomas' Hospital, London SE1 7EH (tel: 071 928 9292, ext 2163)."

Huon Gray writes "The winter meeting of the British Cardiovascular Intervention Society (BCIS) will be held in Southampton on Thursday afternoon 24 September and all day Friday 25 September 1992. Further details regarding the meeting have been distributed to members of BCIS."

Members have first priority for the limited places at our teach-ins, but applications are open to non-members from two months before the event. Those members wishing to ensure reservations for "Emerging Concepts in Atherogenesis" arranged by Michael Davies for 10 November should telephone the office by the middle of September The Workshop on Preventive Cardiology organised by David Wood is booked for 14 October

DOUGLAS CHAMBERLAIN
President, British Cardiac Society,
DUNCAN DYMOND
Secretary, British Cardiac Society,
9 Fitzroy Square,
London W1P 5AH

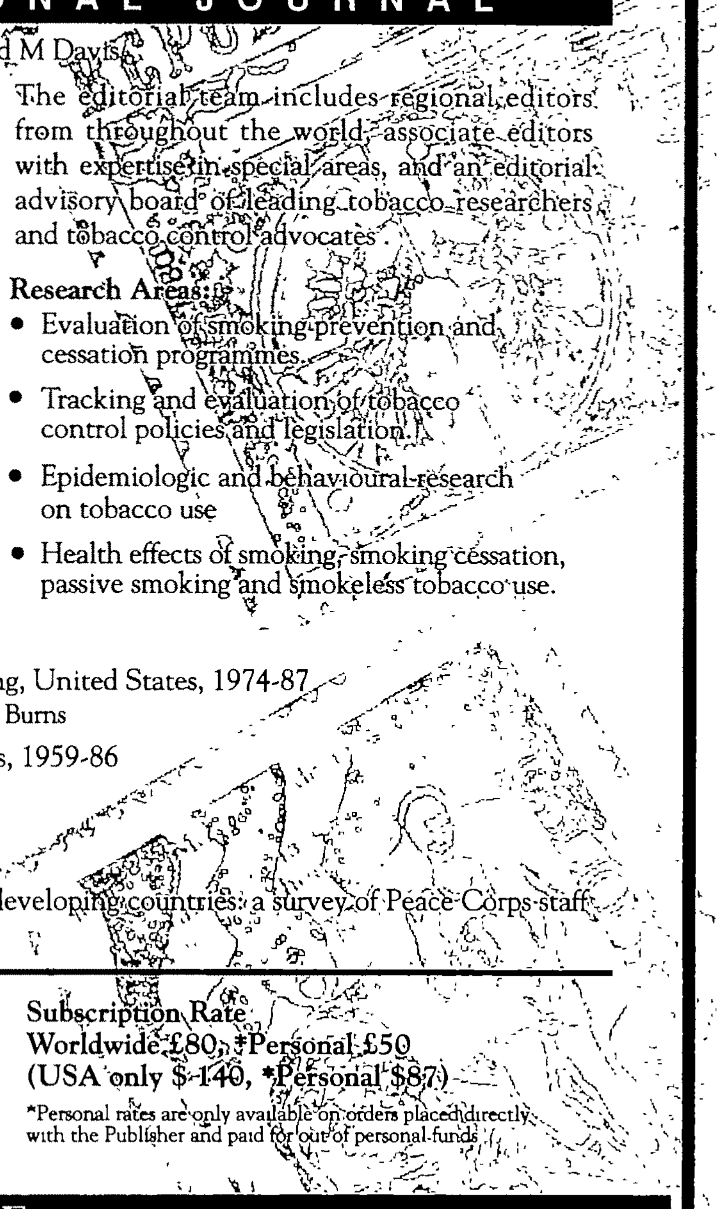
NOTICE

The 1993 Annual Meeting of the **British Cardiac Society** will take place at the Wembley Conference Centre from 18 to 21 May.

TOBACCO CONTROL

AN INTERNATIONAL JOURNAL

Editor: Ronald M Davis



TOBACCO CONTROL is a new quarterly scientific journal launched in March 1992 by the BMJ Publishing Group to consider all aspects of tobacco prevention and control.

The Journal aims to study:

- The nature and extent of tobacco use worldwide
- The effect of tobacco use on health, the economy, the environment and society.
- The efforts of the health community and health advocates to prevent and control tobacco use
- The activities of the tobacco industry and its allies to promote tobacco use

The editorial team includes regional editors from throughout the world, associate editors with expertise in special areas, and an editorial advisory board of leading tobacco researchers and tobacco control advocates.

Research Areas:

- Evaluation of smoking prevention and cessation programmes.
- Tracking and evaluation of tobacco control policies and legislation.
- Epidemiologic and behavioural research on tobacco use
- Health effects of smoking, smoking cessation, passive smoking and smokeless tobacco use.

Papers from Volume One:

- Trends in physicians' giving advice to stop smoking, United States, 1974-87
  E Gilpin, J Pierce, J Goodman, G Giovino, C Berry, D Burns
- Targeting of cigarette advertising in US magazines, 1959-86
  K E Warner, L M Goldenhar
- Recent developments in tobacco litigation, 1991
  R A Daynard
- Support for restricting smoking at workplaces in developing countries: a survey of Peace Corps staff
  T R Eng, S L Emont, T H van der Vlugt

Papers for submission should be sent to.

Ronald M Davis, MD
Editor: Tobacco Control
Michigan Department of Public Health
3423 North Logan Street
PO Box 30195
Lansing, Michigan 48909
USA

Subscription Rate
Worldwide £80, *Personal £50
(USA only $140, *Personal $87)

*Personal rates are only available on orders placed directly with the Publisher and paid for out of personal funds

Order Form

TOBACCO CONTROL
ISSN 0964 4563
PUBLICATION: QUARTERLY

1992 subscription rate:
Worldwide £80, *Personal £50
(USA only $140, *Personal $87)
*Personal rate are only available on orders placed directly with the Publisher and paid for out of personal funds

Please tick

☐ Please send my subscription, start date ____________
☐ Please send me a sample copy
☐ Please send me Instructions to Authors
☐ I enclose a cheque for____________
(Payable to the British Medical Journal)
☐ I wish to pay by credit card.
American Express/Visa(Barclaycard)/Mastercard
(Delete as appropriate)

Card Number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐
MasterCard users should add the numbers appearing above their name

Expiry Date ____________

Signature ____________
(your signature is essential, especially when paying by credit card)

Name *(Capitals)* ____________

Address ____________

____

____

____________ Date ____________

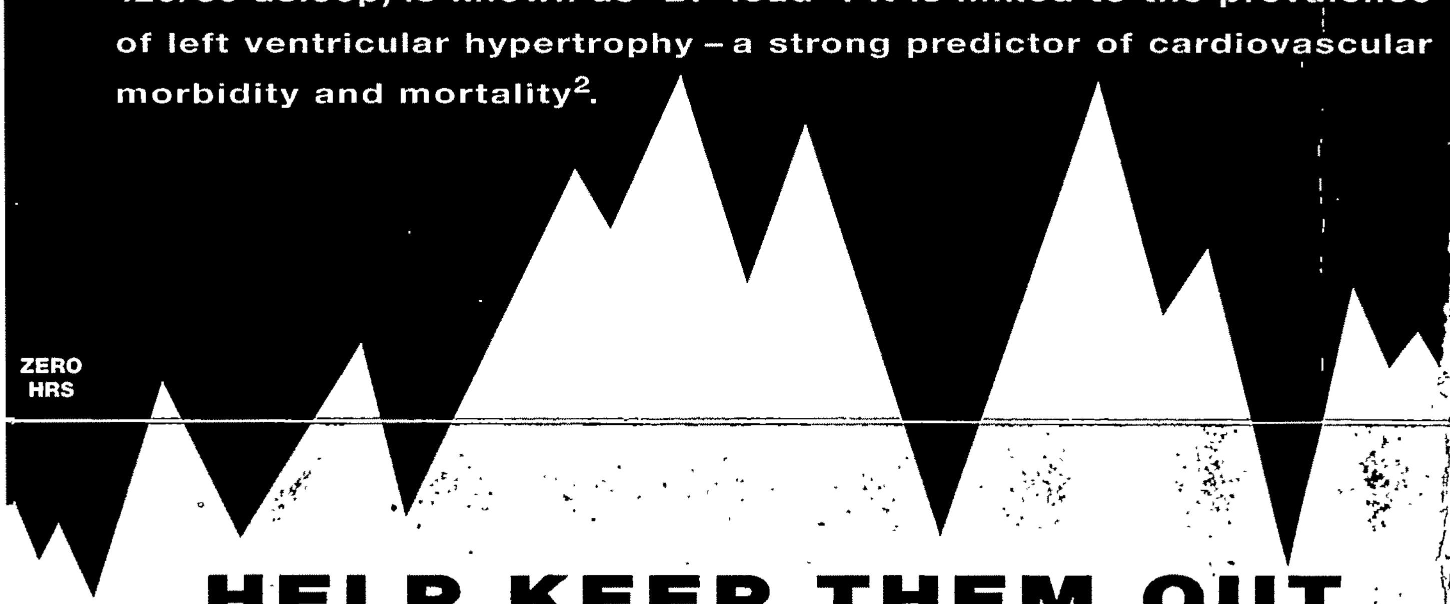
Send orders to. **Journals Marketing Dept., BMJ Publishing Group, BMA House, Tavistock Square, London WC1H 9JR or BMJ Publishing Group, Box No 560B, Kennebunkport, Maine 04046 (Direct Orders Only)**

SJ

RED ALERT

24 HOUR BP LOAD

The length of time a patient's BP is 'in the red' (>140/90 awake, 120/80 asleep) is known as 'BP load'[1]. It is linked to the prevalence of left ventricular hypertrophy – a strong predictor of cardiovascular morbidity and mortality[2].



HELP KEEP THEM OUT OF THE RED AND IN THE GREEN

Zestril

lisinopril ICI

PRESCRIBING NOTES*

Consult data sheet before prescribing.

USE: All grades of essential hypertension and renovascular hypertension. Congestive heart failure (adjunctive therapy).

PRESENTATION: Tablets containing 2.5mg, 5mg, 10mg or 20mg lisinopril ('Zestril').

DOSAGE AND ADMINISTRATION: Hypertension – Adults (including elderly): Initially 2.5mg daily, a 2.5mg dose seldom achieves a therapeutic response, adjust dose according to response. Maintenance usually 10-20mg once-daily. Maximum is 40mg daily. Diuretic-treated patients – if possible stop diuretic 2-3 days before starting 'Zestril'. Resume diuretic later if desired.

Congestive heart failure: Adults (including elderly). Initially 2.5mg daily in hospital under close medical supervision, increasing to 5-20mg once-daily according to response. Monitor blood pressure and renal function.

Renal impairment: May require lower maintenance dosage.

CONTRAINDICATIONS: Pregnancy. Hypersensitivity to 'Zestril'. Patients with history of angioneurotic oedema to previous ACE inhibitor therapy. Patients with aortic stenosis, cor pulmonale or outflow tract obstruction.

PRECAUTIONS: Assessment of renal function is recommended. Symptomatic hypotension may occur, particularly in volume depleted patients and congestive heart failure. Caution in patients with ischaemic heart or cerebrovascular disease, renal insufficiency, renovascular hypertension. Patients with a history of angioedema may be at increased risk of angioedema with an ACE inhibitor. Cough has been reported with ACE inhibitors. Renal impairment (usually [illegible]). Hypotension may occur during surgery or anaesthesia. Caution in nursing mothers. No paediatric experience. Afro-Caribbean patients may show reduced therapeutic response. Symptomatic hypotension can be minimised by discontinuing diuretic prior to 'Zestril'. Interaction with indomethacin and lithium. Potassium supplements, potassium sparing diuretics and potassium containing salt substitutes not recommended. Avoid concomitant use with high-flux dialysis membranes.

SIDE EFFECTS: Hypotension, dizziness, headache, diarrhoea, cough, nausea, fatigue. Less frequently, rash, asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions, myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, palpitation, tachycardia, abdominal pain, dry mouth, hepatitis, jaundice, mood alterations, mental confusion, urticaria, diaphoresis, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, impotence. A symptom complex which may include fever, vasculitis, myalgia, arthralgia/arthritis, positive ANA, elevated ESR, eosinophilia, leukocytosis, rash, photosensitivity or other dermatological manifestations may occur. Increases (usually reversible) in blood urea, serum creatinine, liver enzymes and serum bilirubin. Decreases in haemoglobin and haematocrit have occurred. Hyperkalaemia.

PRODUCT LICENCE NUMBERS AND BASIC NHS COSTS: 'Zestril' 2.5mg (29/0208) 28 tablets, £7.84; 5mg (29/0204) 28 tablets, £9.83, 10mg (29/0205) 28 tablets, £12.13; 20mg (29/0206) 28 tablets, £13.72

'Zestril' is a trademark.

Further information is available from: ICI Pharmaceuticals, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ.

REFERENCE: 1. Kannel WB. Am J Med 1983;75:4-11.

STUART